



ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO BLySB LYMPHOCYTE STIMULATOR PROTEIN

INTRODUCTION

[0001] The present invention relates to antibodies and related molecules that immunospecifically bind to B Lymphocyte Stimulator (BLyS™) protein. The present invention also relates to methods and compositions for detecting, diagnosing, or prognosing a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor expression or inappropriate function of BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor, comprising antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLySB Lymphocyte Stimulator. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor expression or inappropriate BLySB Lymphocyte Stimulator function or BLySB Lymphocyte Stimulator receptor function, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLySB Lymphocyte Stimulator.

BACKGROUND OF THE INVENTION

[0002] B lymphocyte Lymphocyte Sstimulator (BLyS™) protein is a member of the tumor necrosis factor ("TNF") superfamily that induces both *in vivo* and *in vitro* B cell proliferation and differentiation (Moore *et al.*, Science 285: 260-263 (1999)). BLySB Lymphocyte Stimulator is distinguishable from other B cell growth and differentiation factors such as IL-2, IL-4, IL-5, IL-6, IL-7, IL-13, IL-15, CD40L, or CD27L (CD70) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. BLySB Lymphocyte Stimulator expression is not detected on natural killer ("NK") cells, T cells or B cells, but is restricted to cells of myeloid origin. BLySB Lymphocyte Stimulator expression on resting

monocytes is upregulated by interferon-gamma (IFN-gamma). The gene encoding BLySB Lymphocyte Stimulator has been mapped to chromosome 13q34.

[0003] BLySB Lymphocyte Stimulator is expressed as a 285 amino acid type II membrane-bound polypeptide and a soluble 152 amino acid polypeptide (Moore *et al.*, 1999 *supra*). The membrane-bound form of BLySB Lymphocyte Stimulator has a predicted transmembrane spanning domain between amino acid residues 47 and 73. The NH₂-terminus of the soluble form of BLySB Lymphocyte Stimulator begins at Ala¹³⁴ of the membrane-bound form of BLySB Lymphocyte Stimulator. Soluble recombinant BLySB Lymphocyte Stimulator has been shown to induce *in vitro* proliferation of murine splenic B cells and to bind to a cell-surface receptor on these cells (Moore *et al.*, 1999 *supra*). Soluble BLySB Lymphocyte Stimulator administration to mice has been shown to result in an increase in the proportion of CD45R^{dull}, Ly6D^{bright} (also known as ThB) B cells and an increase in serum IgM and IgA levels (Moore *et al.*, 1999 *supra*). Thus, BLySB Lymphocyte Stimulator displays a B cell tropism in both its receptor distribution and biological activity.

[0004] Based upon its expression pattern and biological activity, BLySB Lymphocyte Stimulator has been suggested to be involved in the exchange of signals between B cells and monocytes or their differentiated progeny. The restricted expression patterns of BLySB Lymphocyte Stimulator receptor and ligand suggest that BLySB Lymphocyte Stimulator may function as a regulator of T cell-independent responses in a manner analogous to that of CD40 and CD40L in T cell-dependent antigen activation. As such, antibodies and related molecules that immunospecifically bind to BLySB Lymphocyte Stimulator may find medical utility in, for example, the treatment of B cell disorders associated with autoimmunity, neoplasia, or immunodeficiency syndromes.

SUMMARY OF THE INVENTION

[0005] The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of BLySB Lymphocyte Stimulator. In particular, the invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that

immunospecifically bind to a polypeptide or polypeptide fragment of human BLySB Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or BLySB Lymphocyte Stimulator expressed on human monocytes; murine BLySB Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or BLySB Lymphocyte Stimulator expressed on murine monocytes; rat BLySB Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLySB Lymphocyte Stimulator (*e.g.*, the monkey BLySB Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLySB Lymphocyte Stimulator, or BLySB Lymphocyte Stimulator expressed on monkey monocytes), preferably human BLySB Lymphocyte Stimulator. The present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders associated with aberrant BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor expression or inappropriate function of BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, use of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed, or prognosed with the antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma). The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor expression or inappropriate function of BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, administering to said animal an effective amount of one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that

immunospecifically bind to BLySB Lymphocyte Stimulator. Diseases and disorders which can be prevented, treated or ameliorated by administering an effective amount of an antibody of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0006] Using phage display technology, the present inventors have identified single chain antibody molecules ("scFvs") that immunospecifically bind to BLySB Lymphocyte Stimulator, including scFvs that immunospecifically bind to soluble BLySB Lymphocyte Stimulator, scFvs that immunospecifically bind the membrane-bound form of BLySB Lymphocyte Stimulator, and scFvs that immunospecifically bind to both the soluble form and the membrane-bound form of BLySB Lymphocyte Stimulator. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (*e.g.*, including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[0007] In particular, the invention relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 - 2128, preferably SEQ ID NOS:834 - 872, 1570 - 1595, and 1886 - 1908, and most preferably SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, and 1881 - 1885, as referred to in Table 1 below. In specific embodiments, the present invention relates to scFvs that immunospecifically bind the soluble form of BLySB Lymphocyte Stimulator, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1569, preferably SEQ ID NOS:1570 - 1595, and most preferably SEQ ID NOS: 1563 - 1569, as referred to in Table 1, below. In other embodiments, the present invention also relates to scFvs that immunospecifically bind the membrane-bound form of BLySB Lymphocyte Stimulator, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128, preferably SEQ ID NOS:1886 - 1908, and

most preferably SEQ ID NOS: 1881 - 1885, as referred to in Table 1 below. The present invention further relates to scFvs that immunospecifically bind both the membrane-bound form and soluble form of BLySB Lymphocyte Stimulator, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562, preferably SEQ ID NOS: 834 - 872, and most preferably SEQ ID NOS: 1 - 46, and 321 - 329, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[0008] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of BLySB Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the variable heavy ("VH") domains referred to in Table 1, below, or any one of the variable light ("VL") domains referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. In another preferred embodiment, antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL domain contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of BLySB Lymphocyte

Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0009] The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLySB Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0010] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLySB Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one, two, three or more of the VH complementarity determining regions ("CDRs") (*i.e.*, VH CDR1, VH CDR2, or VH CDR3) referred to in Table 1 and/or any one, two, three or more of the VL CDRs (*i.e.*, VL

CDR1, VL CDR2, or VL CDR3) referred to in Table 1. In one embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1 and/or any one of the VL CDR1s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1 and/or any one of the VL CDR2s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 and/or any one of the VL CDR3s referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0011] In another embodiment, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) immunospecifically bind to a polypeptide or polypeptide fragment of BLySB Lymphocyte Stimulator, and comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, any one of the VH CDR2s referred to in Table 1, and/or any one of the VH CDR3s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, any one of the VL CDR2s referred to in Table 1, and/or any one of the VL CDR3s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, at least one, two, three, four, five, six, or more CDRs that correspond to the same scFv referred to in Table 1, more preferably where CDR1, CDR2, and CDR3 of the VL domain correspond to the same scFv or where CDR1, CDR2, and CDR3 of the VH domain correspond to the same scFv, and most preferably where all six CDRs correspond to the same scFv referred to in Table

1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0012] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that: immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator (e.g., a polypeptide consisting of amino acids 134 - 285 of SEQ ID NO:3228); that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator (e.g., a polypeptide consisting of amino acids 1 - 285 of SEQ ID NO:3228 or a BLySB Lymphocyte Stimulator polypeptide expressed on the surface of monocytes) and/or that immunospecifically bind to both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator. In a preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator. In another preferred embodiment, antibodies of the present invention immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator. In yet another preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically binds to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a

VH domain and a VL domain corresponding to the same scFv disclosed in Table 1, which antibodies immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, or both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator. Nucleic acid molecules encoding these antibodies are also encompassed by the invention. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0013] A VH domain of an amino acid sequence disclosed herein may be combined with

[0014] a VL domain of an amino acid sequence disclosed herein, or other VL domains, to provide a VH/VL pairing representing an antigen-binding site of an antibody. Similarly, a VL domain of an amino acid sequence disclosed herein may be combined with a VH domain of an amino acid sequence disclosed herein, or other VH domains. Further, one or more CDRs disclosed herein may be taken from a VH or VL domain and incorporated into a suitable framework as discussed *infra*.

[0015] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (including derivatives)) comprising, or alternatively consisting of, of VH domains, VL domains and/or CDRs described herein, which antibodies, immunospecifically bind to BLySB Lymphocyte Stimulator (e.g., soluble BLySB Lymphocyte Stimulator and membrane-bound BLySB Lymphocyte Stimulator) and can be routinely assayed for immunospecific binding to BLySB Lymphocyte Stimulator using methods known in the art, such as, for example, the immunoassays disclosed *infra*. Antibodies and antibody fragments or variants (including derivatives) of the invention may include, for example, one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue). These alterations may be made in one or more framework regions and/or one or more CDR's. The antibodies of the invention (including antibody fragments, and variants and

derivative thereof) can be routinely made by methods known in the art. Molecules comprising, or alternatively consisting of, fragments or variants of any of the VH domains, VH CDRs, VL domains, and VL CDRs whose sequences are specifically disclosed herein may be employed in accordance with the present invention. Nucleic acid molecules encoding these antibodies and molecules (including fragments, variants, and derivatives) are also encompassed by the invention.

[0016] The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs). The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs)). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

[0017] The present invention also provides for fusion proteins comprising an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention.

[0018] The present invention also provides for a nucleic acid molecule, generally
[0019] isolated, encoding an antibody (including molecules such as scFvs, which
comprise, or alternatively consist of, an antibody fragment or variant thereof) of the
invention. The present invention also provides a host cell transformed with a nucleic acid
molecule of the invention and progeny thereof. The present invention also provides a
method for the production of an antibody (including a molecule comprising, or
alternatively consisting of, an antibody fragment or variant thereof) of the invention. The
present invention further provides a method of expressing an antibody (including a
molecule comprising, or alternatively consisting of, an antibody fragment or variant
thereof) of the invention from a nucleic acid molecule. These and other aspects of the
invention are described in further detail below.

[0020] The present invention also encompasses methods and compositions for
detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant
BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor expression or
inappropriate BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor
function in an animal, preferably a mammal, and most preferably a human, comprising
using antibodies (including molecules which comprise, or alternatively consist of,
antibody fragments or variants thereof) that immunospecifically bind to BLySB
Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed or
prognosed with the antibodies of the invention include, but are not limited to, immune
disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis,
Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*,
asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and
proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0021] In specific embodiments, the present invention encompasses methods and
compositions for detecting, diagnosing and/or prognosing diseases or disorders associated
with hypergammaglobulinemia (*e.g.*, AIDS, autoimmune diseases, and some
immunodeficiencies). In other specific embodiments, the present invention encompasses
methods and compositions for detecting, diagnosing and/or prognosing diseases or
disorders associated with hypogammaglobulinemia (*e.g.*, an immunodeficiency).

[0022] The present invention further encompasses methods and compositions for
preventing, treating or ameliorating diseases or disorders associated with aberrant BLySB

Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor expression or inappropriate BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0023] In specific embodiments, the present invention encompasses methods and compositions (*e.g.*, antagonistic anti-BLySB Lymphocyte Stimulator antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypergammaglobulinemia (*e.g.*, AIDS, autoimmune diseases, and some immunodeficiency syndromes). In other specific embodiments, the present invention encompasses methods and compositions (*e.g.*, agonistic anti-BLySB Lymphocyte Stimulator antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypogammaglobulinemia (*e.g.*, an immunodeficiency syndrome).

[0024] Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (*e.g.*, IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (*e.g.*, Henloch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (*i.e.*, Hashimoto's thyroiditis, systemic lupus

erythematosis, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomyopathy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders).

[0025] Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

DEFINITIONS

[0026] The term “antibody,” as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody fragments as well as variants (including derivatives) of antibodies and antibody fragments. Examples of molecules which are described by the term “antibody” in this application include, but are not limited to: single chain Fvs (scFvs), Fab fragments, Fab’ fragments, F(ab’)₂, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, either a VL or a VH domain. The term “single chain Fv” or “scFv” as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody. Antibodies that immunospecifically bind to BLySB Lymphocyte Stimulator may have cross-reactivity with other antigens. Preferably, antibodies that immunospecifically bind to BLySB Lymphocyte Stimulator do not cross-react with other antigens. Antibodies that immunospecifically bind to BLySB Lymphocyte Stimulator can be identified, for example, by immunoassays or other techniques known to those of skill in the art, *e.g.*, the immunoassays described in the Examples below.

[0027] Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, Fab fragments, F(ab’) fragments, antiidiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG₁, IgG₂, IgG₃, IgG₄, IgA₁ and IgA₂) or subclass of immunoglobulin molecule.

[0028] Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH CDR, VL domain, or VL CDR having an amino acid sequence of any one of those referred to in Table 1, or a fragment or variant thereof.

[0029] An antibody of the invention “which binds the soluble form of BLySB Lymphocyte Stimulator” is one which binds the 152 amino acid soluble form of the BLySB Lymphocyte Stimulator protein (amino acids 134- 285 of SEQ ID NO:3228). In specific embodiments of the invention, an antibody of the invention “which binds the soluble form of BLySB Lymphocyte Stimulator” does not also bind the membrane-bound

or membrane-associated form of BLySB Lymphocyte Stimulator. Assays which measure binding to the soluble form of BLySB Lymphocyte Stimulator include, but are not limited to, receptor binding inhibition assay or capture of soluble BLySB Lymphocyte Stimulator from solution as described in Examples 8 and 9.

[0030] An antibody of the invention “which binds the membrane-bound form of BLySB Lymphocyte Stimulator” is one which binds the membrane-associated (uncleaved) BLySB Lymphocyte Stimulator protein. In specific embodiments of the invention, an antibody of the invention “which binds the membrane-bound form of BLySB Lymphocyte Stimulator” does not also bind the soluble form of BLySB Lymphocyte Stimulator. Binding to HIS-tagged BLySB Lymphocyte Stimulator (as described herein) in an ELISA is an indicator that an antibody binds the membrane-bound form of BLySB Lymphocyte Stimulator, but should not be relied upon as proof of specificity for the membrane-bound form of BLySB Lymphocyte Stimulator. Assays that may be relied upon as proof of an antibody’s specificity for membrane-bound BLySB Lymphocyte Stimulator, include, but are not limited to, binding to plasma membranes expressing BLySB Lymphocyte Stimulator as described in Example 2. An antibody of the invention “which binds the both the soluble form and the membrane-bound form of BLySB Lymphocyte Stimulator” is one which binds both the membrane-bound form and the soluble form of BLySB Lymphocyte Stimulator.

[0031] The term "variant" as used herein refers to a polypeptide that possesses a similar or identical function as a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, an anti-BLySB Lymphocyte Stimulator antibody or antibody fragment thereof, but does not necessarily comprise a similar or identical amino acid sequence of a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, an anti-BLySB Lymphocyte Stimulator antibody or antibody fragment thereof, or possess a similar or identical structure of a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, an anti-BLySB Lymphocyte Stimulator antibody or antibody fragment thereof. A variant having a similar amino acid refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide comprising, or alternatively consisting of, an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at

least 95% or at least 99% identical to the amino acid sequence of a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, an anti-BLySB Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1) described herein; (b) a polypeptide encoded by a nucleotide sequence, the complementary sequence of which hybridizes under stringent conditions to a nucleotide sequence encoding a BLySB Lymphocyte Stimulator polypeptide (e.g., SEQ ID NO:3228), a fragment of BLySB Lymphocyte Stimulator, an anti-BLySB Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein, of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99%, identical to the nucleotide sequence encoding a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, an anti-BLySB Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein. A polypeptide with similar structure to a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, an anti-BLySB Lymphocyte Stimulator antibody or antibody fragment thereof, described herein refers to a polypeptide that has a similar secondary, tertiary or quarternary structure of a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, an anti-BLySB Lymphocyte Stimulator antibody, or antibody fragment thereof, described herein. The structure of a polypeptide can determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

[0032] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = number of identical overlapping positions/total number of positions x 100%). In one embodiment, the two sequences are the same length.

[0033] The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 87:2264-2268(1990), modified as in Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 90:5873-5877(1993). The BLASTn and BLASTx programs of Altschul, et al. *J. Mol. Biol.* 215:403-410(1990) have incorporated such an algorithm. BLAST nucleotide searches can be performed with the BLASTn program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTx program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. *Nucleic Acids Res.* 25:3389-3402(1997). Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-BLAST programs, the default parameters of the respective programs (*e.g.*, BLASTx and BLASTn) can be used. (See <http://www.ncbi.nlm.nih.gov>.)

[0034] Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). The ALIGN program (version 2.0) which is part of the GCG sequence alignment software package has incorporated such an algorithm. Other algorithms for sequence analysis known in the art

include ADVANCE and ADAM as described in Torellis and Robotti *Comput. Appl. Biosci.*, 10 :3-5(1994); and FASTA described in Pearson and Lipman *Proc. Natl. Acad. Sci.* 85:2444-8(1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

[0035] The term "derivative" as used herein, refers to a variant polypeptide of the invention that comprises, or alternatively consists of, an amino acid sequence of a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, or an antibody of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator, which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, an antibody that immunospecifically binds to BLySB Lymphocyte Stimulator which has been modified, *e.g.*, by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, or an anti-BLySB Lymphocyte Stimulator antibody, may be modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, or an anti-BLySB Lymphocyte Stimulator antibody, may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, or an anti-BLySB Lymphocyte Stimulator antibody, may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a BLySB Lymphocyte Stimulator polypeptide, a fragment of BLySB Lymphocyte Stimulator, or an anti-BLySB Lymphocyte Stimulator antibody, described herein.

[0036] The term "epitopes" as used herein refers to portions of BLySB Lymphocyte Stimulator having antigenic or immunogenic activity in an animal, preferably a mammal. An epitope having immunogenic activity is a portion of BLySB Lymphocyte Stimulator that elicits an antibody response in an animal. An eptiope having antigenic activity is a

portion of BLySB Lymphocyte Stimulator to which an antibody immunospecifically binds as determined by any method known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic.

[0037] The term "fragment" as used herein refers to a polypeptide comprising an amino acid sequence of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, at least 150 amino acid residues, at least 175 amino acid residues, at least 200 amino acid residues, or at least 250 amino acid residues, of the amino acid sequence of BLySB Lymphocyte Stimulator, or an anti-BLySB Lymphocyte Stimulator antibody (including molecules such as scFv's, that comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically binds to BLySB Lymphocyte Stimulator.

[0038] The term "fusion protein" as used herein refers to a polypeptide that comprises, or alternatively consists of, an amino acid sequence of an anti-BLySB Lymphocyte Stimulator antibody of the invention and an amino acid sequence of a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain).

[0039] The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

DESCRIPTION OF THE FIGURES

[0040] Figure 1. ELISA results for three scFvs, I006E07, I008D05 and I016F04, that immunospecifically bind to U937 membranes, but not to bind to or cross-react with TNF-alpha or BSA.

[0041] Figure 2. The results for three scFvs, I016H07, I001C09 and I018D07, in a receptor inhibition assay.

[0042] Figure 3. ELISA results for two scFvs (I022D01 and I031F02) demonstrating their ability to bind to human BLySB Lymphocyte Stimulator and to cross-react with mouse BLySB Lymphocyte Stimulator, but not to bind to or cross-react with other antigens of the TNF ligand family.

[0043] Figure 4. ELISA results for three scFvs (I031F09, I050A12, and I051C04) binding to U937 plasma membranes when either BLySB Lymphocyte Stimulator or TNF-alpha is used as a competitor.

[0044] Figure 5. Kinetic analysis of scFv antibody I003C02. A dilution series of I003C02 from 3nM to 825nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

[0045] Figure 6. Typical titration curves for two scFv antibodies (I007F11 and I050A07) are shown in Figure 6. Unlabelled BLySB Lymphocyte Stimulator competed for binding to its receptor with an IC₅₀ value of 0.8 nM. The IC₅₀ values for I007F11 and I050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

[0046] Figure 7. ELISA results for three scFvs clones (I074B12, I075F12 and I075A02) that immunospecifically bind to immobilized BLySB Lymphocyte Stimulator, but not to U937 plasma membranes, TNF-alpha or BSA. As a control, a phage antibody that recognizes TNF α , is also shown in Figure 7.

[0047] Figure 8. The results for two scFvs (I025B09 and I026C04) in a receptor inhibition assay.

[0048] Figure 9. ELISA results for two scFvs clones (I067F05 and I078D02) demonstrating their ability to bind to immobilized human BLySB Lymphocyte Stimulator and to cross-react with immobilized mouse BLySB Lymphocyte Stimulator, but not to bind to or cross-react with other antigens of the TNF ligand family.

[0049] As a control, a phage antibody that recognizes TNF α , is also shown in Figure 7.

[0050] Figure 10. Kinetic analysis of scFV antibody I002A01. A dilution series of I002A01 from 3nM to 1650nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

[0051] Figure 11. Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in Figure 11. Unlabelled BLySB Lymphocyte Stimulator competed for binding to

its receptor with an inhibitory constant 50 (IC_{50}) value of 0.66 nM. The IC_{50} values for I0068C06 and I074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

[0052] Figure 12. ELISA results for three clones (I079C01, I081C10 and I082A02) demonstrating their ability to bind histidine-tagged BLySB Lymphocyte Stimulator, U937 plasma membranes, but not to bind immobilized biotinylated BLySB Lymphocyte Stimulator.

[0053] Figure 13. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to U937 plasma membranes when either histidine-tagged BLySB Lymphocyte Stimulator or biotinylated BLySB Lymphocyte Stimulator is used as a competitor.

[0054] Figure 14. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in Figure 14. An anti-TNF α antibody that does not recognize BLySB Lymphocyte Stimulator was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

[0055] Figure 15. A typical example of the binding curves generated for the scFv antibody I082C03 is shown in Figure 15. The off-rate for this clone was calculated as $2 \times 10^{-3} \text{ s}^{-1}$. The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv.

[0056] Figure 16. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to P388 plasma membranes when either histidine-tagged BLySB Lymphocyte Stimulator or biotinylated BLySB Lymphocyte Stimulator is used as a competitor.

DETAILED DESCRIPTION OF THE INVENTION

[0057] The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator or a fragment or variant of BLySB Lymphocyte Stimulator. In particular, the invention provides antibodies such as, for example, single chain Fvs (scFvs) having an amino acid sequence of any one of SEQ ID NOS:1 - 2128, as referred to in Table 1. In particular, the present invention encompasses antibodies that immunospecifically bind to a polypeptide, a polypeptide

fragment or variant, or an epitope of human BLySB Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or BLySB Lymphocyte Stimulator expressed on human monocytes; murine BLySB Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or BLySB Lymphocyte Stimulator expressed on murine monocytes; rat BLySB Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLySB Lymphocyte Stimulator (*e.g.*, the monkey BLySB Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLySB Lymphocyte Stimulator, or BLySB Lymphocyte Stimulator expressed on monkey monocytes) (as determined by immunoassays known in the art for assaying specific antibody-antigen binding).

[0058] The polypeptide sequence shown in SEQ ID NO:3228 was obtained by sequencing and translating the cDNA of the HNEDU15 clone which was deposited on October 22, 1996 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, and assigned ~~ATCC~~ATCCTM Accession No. 97768. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The ~~ATCC~~ATCCTM deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0059] The polypeptide sequence shown in SEQ ID NO:3229 was obtained by sequencing and translating the cDNA of the HDPMC52 clone, which was deposited on December 10, 1998 at the American Type Culture Collection, and assigned ~~ATCC~~ATCCTM Accession No. 203518. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The ~~ATCC~~ATCCTM deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0060] The BLySB Lymphocyte Stimulator polypeptides bound by the antibodies of the invention may be in monomers or multimers (*i.e.*, dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to antibodies that bind monomers and multimers of the BLySB Lymphocyte Stimulator polypeptides of the invention, their preparation, and compositions (preferably, pharmaceutical compositions) containing them. In specific embodiments, the antibodies of the invention bind BLySB Lymphocyte

Stimulator monomers, dimers, trimers or tetramers. In additional embodiments, the antibodies of the invention bind at least dimers, at least trimers, or at least tetramers of BLySB Lymphocyte Stimulator.

[0061] Multimeric BLySB Lymphocyte Stimulator bound by the antibodies of the invention may be homomers or heteromers. A BLySB Lymphocyte Stimulator homomer, refers to a multimer containing only BLySB Lymphocyte Stimulator polypeptides (including BLySB Lymphocyte Stimulator fragments, variants, and fusion proteins, as described herein). These homomers may contain BLySB Lymphocyte Stimulator polypeptides having identical or different amino acid sequences. In specific embodiments, the antibodies of the invention bind a BLySB Lymphocyte Stimulator homodimer (e.g., containing two BLySB Lymphocyte Stimulator polypeptides having identical or different amino acid sequences) or a BLySB Lymphocyte Stimulator homotrimer (e.g., containing three BLySB Lymphocyte Stimulator polypeptides having identical or different amino acid sequences). In a preferred embodiment, the antibodies of the invention bind homotrimers of BLySB Lymphocyte Stimulator. In additional embodiments, the antibodies of the invention bind a homomeric BLySB Lymphocyte Stimulator multimer which is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[0062] Heteromeric BLySB Lymphocyte Stimulator refers to a multimer containing heterologous polypeptides (i.e., polypeptides of a different protein) in addition to the BLySB Lymphocyte Stimulator polypeptides of the invention. In a specific embodiment, the antibodies of the invention bind a BLySB Lymphocyte Stimulator heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of the invention bind a heteromeric BLySB Lymphocyte Stimulator multimer which is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer. In highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising both BLySB Lymphocyte Stimulator polypeptides and APRIL polypeptides (SEQ ID NO:3239; GenBank Accession No. AF046888; PCT International Publication Number WO97/33902; J. Exp. Med. 188(6):1185-1190) or fragments or variants thereof. In other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising one BLySB Lymphocyte Stimulator polypeptide (including fragments or variants) and two APRIL polypeptides (including fragments or variants). In still other highly preferred embodiments, the antibodies of the invention bind a heterotrimer

comprising two BLySB Lymphocyte Stimulator polypeptides (including fragments or variants) and one APRIL polypeptide (including fragments or variants). In a further nonexclusive embodiment, the heteromers bound by the antibodies of the invention contain CD40 ligand polypeptide sequence(s), or biologically active fragment(s) or variant(s) thereof.

[0063] In particularly preferred embodiments, the antibodies of the invention bind homomeric, especially homotrimeric, BLySB Lymphocyte Stimulator polypeptides, wherein the individual protein components of the multimers consist of the mature form of BLySB Lymphocyte Stimulator (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof. In other specific embodiments, antibodies of the invention bind heteromeric, especially heterotrimeric, BLySB Lymphocyte Stimulator polypeptides such as a heterotrimer containing two BLySB Lymphocyte Stimulator polypeptides and one APRIL polypeptide or a heterotrimer containing one BLySB Lymphocyte Stimulator polypeptide and two APRIL polypeptides, and wherein the individual protein components of the BLySB Lymphocyte Stimulator heteromer consist of the mature extracellular soluble portion of either BLySB Lymphocyte Stimulator (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof, or the mature extracellular soluble portion APRIL (e.g., amino acid residues 105-250 of SEQ ID NO:3239) or fragments or variants thereof.

[0064] In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLySB Lymphocyte Stimulator monomeric protein. In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLySB Lymphocyte Stimulator multimeric, especially trimeric, protein. In other embodiments, antibodies of the invention bind conformational epitopes that arise from the juxtaposition of BLySB Lymphocyte Stimulator with a heterologous polypeptide, such as might be present when BLySB Lymphocyte Stimulator forms heterotrimers (e.g., with APRIL polypeptides (e.g., SEQ ID NO:3239)), or in fusion proteins between BLySB Lymphocyte Stimulator and a heterologous polypeptide.

[0065] BLySB Lymphocyte Stimulator multimers bound by the antibodies of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus,

in one embodiment, B_{LY}S_B Lymphocyte Stimulator multimers, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, B_{LY}S_B Lymphocyte Stimulator heteromultimers, such as, for example, B_{LY}S_B Lymphocyte Stimulator heterotrimers or B_{LY}S_B Lymphocyte Stimulator heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, B_{LY}S_B Lymphocyte Stimulator multimers are formed by covalent associations with and/or between the B_{LY}S_B Lymphocyte Stimulator polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:3228 or SEQ ID NO:3229). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a B_{LY}S_B Lymphocyte Stimulator fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a B_{LY}S_B Lymphocyte Stimulator-Fc fusion protein. In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from CD40L, or a soluble fragment thereof. In another embodiment, two or B_{LY}S_B Lymphocyte Stimulator polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple B_{LY}S_B Lymphocyte Stimulator polypeptides separated by peptide linkers may be produced using conventional

recombinant DNA technology.

[0066] In one embodiment, antibodies of the invention immunospecifically bind a BLySB Lymphocyte Stimulator polypeptide having the amino acid sequence of SEQ ID NO:3228 or as encoded by the cDNA clone contained in ATCCATCC™ No. 97768, or a polypeptide comprising a portion (i.e., a fragment) of the above polypeptides. In another embodiment, the invention provides an antibody that binds an isolated BLySB Lymphocyte Stimulator polypeptide having the amino acid sequence of SEQ ID NO:3229 or the amino acid sequence encoded by the cDNA clone contained in ATCCATCC™ No. 203518, or a an antibody that binds polypeptide comprising a portion (i.e, fragment) of the above polypeptides.

[0067] Antibodies of the present invention immunospecifically bind to polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCCATCC™ accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCCATCC™ accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

[0068] Additionally, antibodies of the present invention bind polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCCATCC™ accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCCATCC™ accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

[0069] In addition, antibodies of the invention bind polypeptides or polypeptide fragments comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NOS: 3230 through 3237.

[0070] In specific embodiments, the antibodies of the present invention

immunospecifically bind polypeptide fragments including polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:3228, encoded by the cDNA contained in the deposited clone, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by the antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, and/or 251 to 285 of SEQ ID NO:3228. Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length.

[0071] In specific embodiments, antibodies of the present invention bind polypeptide fragments comprising, or alternatively consisting of, amino acid residues: 1-46, 31-44, 47-72, 73-285, 73-83, 94-102, 148-152, 166-181, 185-209, 210-221, 226-237, 244-249, 253-265, and/or 277-285 of SEQ ID NO:3228.

[0072] It will be recognized by one of ordinary skill in the art that mutations targeted to regions of a BLySB Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 which encompass the nineteen amino acid residue insertion which is not found in the BLySB Lymphocyte Stimulator polypeptide sequence of SEQ ID NO:3229 (i.e., amino acid residues Val-142 through Lys-160 of the sequence of SEQ ID NO:3229) may affect the observed biological activities of the BLySB Lymphocyte Stimulator polypeptide. More specifically, a partial, non-limiting and non-exclusive list of such residues of the BLySB Lymphocyte Stimulator polypeptide sequence which may be targeted for mutation includes the following amino acid residues of the BLySB Lymphocyte Stimulator polypeptide sequence as shown in SEQ ID NO:3228: V-142; T-143; Q-144; D-145; C-146; L-147; Q-148; L-149; I-150; A-151; D-152; S-153; E-154; T-155; P-156; T-157; I-158; Q-159; and K-160. Thus, in specific embodiments, antibodies of the present invention that bind BLySB Lymphocyte Stimulator polypeptides which have one or more mutations in the region from V-142 through K-160 of SEQ ID NO:3228 are contemplated.

[0073] Polypeptide fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single

continuous region. Representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 15, 16-30, 31-46, 47-55, 56-72, 73-104, 105-163, 163-188, 186-210 and 210-284 of the amino acid sequence disclosed in SEQ ID NO:3228. Additional representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 143, 1-150, 47-143, 47-150, 73-143, 73-150, 100-150, 140-145, 142-148, 140-150, 140-200, 140-225, and 140-266 of the amino acid sequence disclosed in SEQ ID NO:3229. Moreover, polypeptide fragments that may be bound by antibodies of the present invention, can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini.

[0074] Additional preferred embodiments encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLySB Lymphocyte Stimulator (e.g., amino acid residues 1-46 of SEQ ID NO:3228), the predicted transmembrane domain of BLySB Lymphocyte Stimulator (e.g., amino acid residues 47-72 of SEQ ID NO:3228), the predicted extracellular domain of BLySB Lymphocyte Stimulator (e.g., amino acid residues 73-285 of SEQ ID NO:3228), the mature soluble extracellular domain of BLySB Lymphocyte Stimulator (e.g., amino acids residues 134-285 of SEQ ID NO:3228), the predicted TNF conserved domain of BLySB Lymphocyte Stimulator (e.g., amino acids 191 to 284 of SEQ ID NO:3228), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLySB Lymphocyte Stimulator (amino acid residues 1-46 fused to amino acid residues 73-285 of SEQ ID NO:3228).

[0075] Further additional preferred embodiments encompass polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLySB Lymphocyte Stimulator (amino acid residues 1-46 of SEQ ID NO:3229), the predicted transmembrane domain of BLySB Lymphocyte Stimulator (amino acid residues 47-72 of SEQ ID NO:3229), the predicted extracellular domain of BLySB Lymphocyte Stimulator (amino acid residues 73-266 of SEQ ID NO:3229), the predicted TNF conserved domain

of BLySB Lymphocyte Stimulator (amino acids 172 to 265 of SEQ ID NO:3229), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLySB Lymphocyte Stimulator (amino acid residues 1-46 fused to amino acid residues 73-266 of SEQ ID NO:3229).

[0076] Certain additional embodiments of the invention encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted beta-pleated sheet regions of the BLySB Lymphocyte Stimulator polypeptides of SEQ ID NO:3228 and SEQ ID NO:3229. These polypeptide fragments comprising the beta-pleated sheets of BLySB Lymphocyte Stimulator comprise, or alternatively consist of, amino acid residues Gln-144 to Ala-151, Phe-172 to Lys-173, Ala-177 to Glu-179, Asn-183 to Ile-185, Gly-191 to Lys-204, His-210 to Val-219, Leu-226 to Pro-237, Asn-242 to Ala-251, Gly-256 to Ile-263 and/or Val-276 to Leu-284 of SEQ ID NO:3228. In another, nonexclusive embodiment, these polypeptide fragments comprising the beta-pleated sheets of BLySB Lymphocyte Stimulator comprise, or alternatively consist of, amino acid residues Phe-153 to Lys-154, Ala-158 to Glu-160, Asn-164 to Ile-166, Gly-172 to Lys-185, His-191 to Val-200, Leu-207 to Pro-218, Asn-223 to Ala-232, Gly-237 to Ile-244 and/or Val-257 to Leu-265 of SEQ ID NO:3229.

[0077] A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences of the invention includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228. Other combinations of amino acids sequences that may be bound by the antibodies of the invention may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] fused to [Val-142 to Lys-160] of (SEQ ID NO:3228). Other combinations of amino acids sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or

polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228 fused to a FLAG tag ; or [Met-1 to Lys-113] of SEQ ID NO:3228 fused to [Leu-114 to Thr-141] of SEQ ID NO:3228 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Val-142 to Lys-160] of SEQ ID NO:3228 fused to [Gly-161 to Gln-198] of SEQ ID NO:3228 fused to [Val-199 to Ala-248] of SEQ ID NO:3228 fused to [Gly-249 to Leu-285] of SEQ ID NO:3228).

[0078] A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; [Met-1 to Lys-113] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229. Other of amino acids sequences that may be bound by the antibodies of the invention combinations may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] fused to [Gly-142 to Gln-179] of SEQ ID NO:3229). Other combinations of amino acid sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229 fused to a FLAG tag (SEQ ID NO:3238) or, [Met-1 to Lys-113] of SEQ ID NO:3229 fused to [Leu-114 to Thr-141] of SEQ ID NO:3229 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Gly-142 to Gln-179] of SEQ ID NO:3229 fused to [Val-180 to Ala-229] of SEQ ID NO:3229 fused to [Gly-230 to Leu-266] of SEQ ID NO:3229).

[0079] Additional embodiments of the invention encompass antibodies that bind BLySB Lymphocyte Stimulator polypeptide fragments comprising, or alternatively consisting of, functional regions of polypeptides of the invention, such as the Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and

hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index set out in Tables 9 and 10 and as described herein. In a preferred embodiment, the polypeptide fragments bound by the antibodies of the invention are antigenic (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of a complete (i.e., full-length) BLySB Lymphocyte Stimulator polypeptide (e.g., SEQ ID NOS:3228 and 3229).

[0080] The data representing the structural or functional attributes of the BLySB Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 (Table 9) or the BLySB Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 (Table 10), as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III represents the results of a Garnier Robson analysis of beta sheet regions; Column IV represents the results of a Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column IX represents a Hopp-Woods hydrophobicity plot; Column X represents the results of an Eisenberg analysis of alpha amphipathic regions; Column XI represents the results of an Eisenberg analysis of beta amphipathic regions; Column XII represents the results of a Karplus-Schultz analysis of flexible regions; Column XIII represents the Jameson-Wolf antigenic index score; and Column XIV represents the Emini surface probability plot.

[0081] In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Tables 9 and 10 can be used to determine regions of the BLySB Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 (Table 9) or the BLySB Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 (Table 10) which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide

in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0082] The above-mentioned preferred regions set out in Tables 9 and 10 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Tables 9 and 10, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions. Preferably, antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides or BLySB Lymphocyte Stimulator polypeptide fragments and variants comprising regions of BLySB Lymphocyte Stimulator that combine several structural features, such as several (e.g., 1, 2, 3 , or 4) of the same or different region features set out above and in Tables 9 and 10.

Table 9

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	T	T	.	1.09	-1.80	.	*	F	3.06	2.72
Asp	44	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	-2.00	1.23	.	.	.	-0.60	0.19

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Thr	51	A	A	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	T	.	-0.50	0.16	.	*	.	0.10	0.55
Gln	73	A	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	T	.	-0.76	0.09	.	*	F	0.25	0.73
Leu	76	A	A	-0.06	0.09	.	*	F	-0.15	0.35
Ala	77	A	A	0.17	-0.31	.	*	.	0.30	0.69
Ser	78	A	A	0.17	-0.24	.	*	.	0.30	0.42
Leu	79	A	A	-0.30	-0.24	.	*	.	0.30	0.88
Arg	80	A	A	-0.30	-0.24	.	*	.	0.30	0.72
Ala	81	A	A	0.17	-0.34	.	*	.	0.30	0.93
Glu	82	A	A	0.72	-0.30	.	*	.	0.45	1.11
Leu	83	A	A	0.99	-0.49	.	*	.	0.30	0.77
Gln	84	A	A	1.21	0.01	.	*	.	-0.15	1.04
Gly	85	A	A	1.10	0.01	*	*	.	-0.30	0.61
His	86	A	A	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	0.92	-0.67	.	*	.	0.75	1.47
Ala	88	A	A	1.52	-0.39	.	*	.	0.45	1.22
Glu	89	A	A	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	-0.14	0.21	.	*	.	-0.10	0.36
Gly	96	A	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	-0.28	-0.21	.	*	F	0.65	0.71
Lys	99	A	A	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	0.66	-0.46	.	.	F	0.60	1.01

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	101	A	A	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	-0.80	0.49	.	*	.	-0.60	0.38
Thr	109	A	A	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	C	0.34	-0.00	.	.	F	2.20	1.47
Ala	119	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	C	1.66	-0.60	*	.	F	1.49	0.89
Gln	136	C	1.66	-0.60	*	.	F	1.83	0.79
Gly	137	T	C	1.30	-0.60	*	.	F	2.52	1.35
Pro	138	T	C	0.33	-0.61	*	.	F	2.86	2.63
Glu	139	T	T	.	0.61	-0.61	*	.	F	3.40	1.13
Glu	140	A	T	.	1.47	-0.53	*	.	F	2.66	1.64
Thr	141	A	1.47	-0.56	.	.	F	2.12	1.84
Val	142	A	1.14	-0.99	.	.	F	1.78	1.77
Thr	143	A	T	.	0.54	-0.41	.	.	F	1.19	0.55
Gln	144	A	T	.	0.54	0.27	*	.	F	0.25	0.31
Asp	145	A	T	.	-0.27	0.19	*	.	F	0.25	0.73
Cys	146	A	T	.	-0.84	0.23	*	.	.	0.10	0.42
Leu	147	A	A	-0.58	0.43	*	.	.	-0.60	0.17
Gln	148	A	A	-0.27	0.53	*	.	.	-0.60	0.10
Leu	149	A	A	-0.57	0.53	*	*	.	-0.30	0.32
Ile	150	A	A	-0.57	0.34	*	.	.	0.30	0.52

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala	151	.	A	C	-0.21	-0.34	.	*	.	1.40	0.52
Asp	152	T	T	.	0.39	-0.26	.	*	F	2.45	0.91
Ser	153	T	C	0.08	-0.51	.	.	F	3.00	2.00
Glu	154	T	C	-0.00	-0.71	.	.	F	2.70	2.86
Thr	155	T	C	0.89	-0.53	*	.	F	2.40	1.20
Pro	156	.	.	.	B	.	.	C	1.52	-0.13	*	.	F	1.56	1.55
Thr	157	.	.	.	B	T	.	.	1.18	-0.51	*	.	F	1.92	1.79
Ile	158	A	.	.	B	.	.	.	1.18	-0.09	.	.	F	1.08	1.23
Gln	159	T	T	.	0.93	-0.19	.	.	F	2.04	1.07
Lys	160	T	T	.	0.93	0.14	*	.	F	1.60	1.16
Gly	161	T	T	.	0.44	0.14	*	.	F	1.44	2.38
Ser	162	T	T	.	-0.10	0.24	*	.	F	1.28	1.19
Tyr	163	.	.	.	B	T	.	.	0.58	0.49	*	.	.	0.12	0.44
Thr	164	.	.	B	B	.	.	.	0.29	0.91	*	.	.	-0.44	0.69
Phe	165	.	.	B	B	.	.	.	-0.57	1.40	*	.	.	-0.60	0.54
Val	166	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	167	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	168	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	169	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29
Leu	170	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ter	171	A	0.19	0.46	*	.	.	0.20	0.71
Phe	172	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	173	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	174	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly	175	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	176	A	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	177	A	A	1.66	-1.00	*	.	F	1.35	0.76
Leu	178	A	A	1.61	-1.00	.	.	F	1.20	1.54
Glu	179	A	A	1.50	-1.43	.	.	F	0.90	1.98
Glu	180	A	A	1.89	-1.41	*	.	F	0.90	3.16
Lys	181	A	A	1.30	-1.91	*	.	F	0.90	7.66
Glu	182	A	A	1.08	-1.91	.	.	F	0.90	3.10
Asn	183	A	A	1.03	-1.23	*	*	F	0.90	1.48
Lys	184	A	A	1.08	-0.59	*	.	F	0.75	0.55
Ile	185	A	A	1.08	-0.59	*	*	.	0.60	0.63
Leu	186	A	A	0.72	-0.59	*	*	.	0.60	0.68
Val	187	A	A	0.38	-0.50	.	*	.	0.30	0.49
Lys	188	A	A	0.13	-0.07	*	*	F	0.45	0.69
Glu	189	A	T	.	-0.61	0.00	*	*	F	0.40	1.32
Thr	190	T	T	.	-0.42	0.10	.	*	F	0.80	1.54
Gly	191	T	T	.	-0.50	0.24	*	.	F	0.65	0.67
Tyr	192	T	T	.	0.11	0.93	*	*	.	0.20	0.27
Phe	193	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.60	0.29
Phe	194	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.60	0.29
Ile	195	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	196	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	197	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	198	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	199	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	200	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Tyr	201	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	202	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	203	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	204	A	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	205	A	A	0.90	-0.16	.	.	F	0.60	1.73
Tyr	206	A	A	1.11	-0.21	.	.	.	0.45	1.03
Ala	207	A	A	0.61	0.29	.	.	.	-0.30	0.70
Met	208	A	A	-0.28	0.97	.	.	.	-0.60	0.40
Gly	209	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	210	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31
Leu	211	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	212	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln	213	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg	214	A	A	.	B	.	.	.	1.08	-0.59	.	*	F	0.90	1.62
Lys	215	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys	216	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val	217	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	218	.	A	B	B	.	.	.	0.91	-0.00	.	*	.	0.30	0.29
Val	219	.	A	B	B	.	.	.	0.80	-0.00	*	*	.	0.30	0.25
Phe	220	.	.	B	B	.	.	.	-0.06	-0.00	*	.	.	0.30	0.57
Gly	221	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	222	A	-0.36	-0.07	*	.	.	0.50	0.63
Glu	223	A	-1.18	-0.03	*	.	.	0.50	0.60
Leu	224	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	225	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	226	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	227	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	228	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	229	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	230	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	231	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	232	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	233	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	234	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	235	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met	236	.	.	.	B	.	.	C	0.01	0.01	*	.	F	0.20	2.44
Pro	237	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	238	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	239	C	1.36	0.04	*	.	F	1.12	1.82
Leu	240	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	241	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	242	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	243	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	244	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	245	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	246	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	247	A	-0.42	0.71	.	.	.	-0.40	0.18
Ala	248	A	A	-0.38	0.83	.	.	.	-0.60	0.34
Gly	249	A	A	-0.89	0.26	.	.	.	-0.30	0.43
Ile	250	A	A	-0.22	0.19	*	.	.	-0.30	0.27

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala	251	A	A	0.02	-0.20	*	.	.	0.30	0.46
Lys	252	A	A	-0.02	-0.70	.	.	.	0.60	0.80
Leu	253	A	A	0.57	-0.70	.	.	F	0.90	1.13
Glu	254	A	A	0.91	-1.39	.	.	F	0.90	1.87
Glu	255	A	A	0.99	-1.89	.	.	F	0.90	1.62
Gly	256	A	A	1.58	-1.20	.	*	F	0.90	1.62
Asp	257	A	A	0.72	-1.49	.	*	F	0.90	1.62
Glu	258	A	A	0.94	-0.80	*	*	F	0.75	0.77
Leu	259	A	A	0.06	-0.30	*	*	.	0.30	0.79
Gln	260	A	A	-0.16	-0.04	*	.	.	0.30	0.33
Leu	261	A	A	0.30	0.39	*	.	.	-0.30	0.30
Ala	262	A	A	0.30	0.39	*	.	.	-0.30	0.70
Ile	263	A	A	0.30	-0.30	.	*	.	0.30	0.70
Pro	264	A	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg	265	A	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu	266	A	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn	267	A	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala	268	A	0.81	-0.63	*	*	.	0.95	1.05
Gln	269	A	1.02	0.06	*	*	.	-0.10	0.50
Ile	270	A	0.57	0.06	.	*	.	0.15	0.52
Ser	271	C	0.57	0.09	.	*	.	0.60	0.51
Leu	272	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp	273	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	274	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	275	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	276	A	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	277	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	278	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	279	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	280	A	A	-1.58	0.67	.	*	.	-0.60	0.28
Ala	281	A	A	-1.53	0.87	.	*	.	-0.60	0.27
Leu	282	A	A	-1.61	0.77	*	.	.	-0.60	0.26
Lys	283	A	A	-1.30	0.41	*	.	.	-0.60	0.33
Leu	284	A	A	-0.99	0.41	.	.	.	-0.60	0.42
Leu	285	A	A	-1.03	0.34	*	.	.	-0.30	0.65

Table 10

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	T	T	.	1.09	-1.80	*	*	F	3.06	2.72
Asp	44	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	-2.00	1.23	.	.	.	-0.60	0.19

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Thr	51	A	A	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	T	.	-0.50	0.16	.	.	.	0.10	0.55
Gln	73	A	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	T	.	-0.76	0.09	.	*	F	0.25	0.73
Leu	76	A	A	-0.06	0.09	.	*	F	-0.15	0.35
Ala	77	A	A	0.17	-0.31	.	*	.	0.30	0.69
Ser	78	A	A	0.17	-0.24	.	*	.	0.30	0.42
Leu	79	A	A	-0.30	-0.24	.	*	.	0.30	0.88
Arg	80	A	A	-0.30	-0.24	.	*	.	0.30	0.72
Ala	81	A	A	0.17	-0.34	.	*	.	0.30	0.93
Glu	82	A	A	0.72	-0.30	.	*	.	0.45	1.11
Leu	83	A	A	0.99	-0.49	.	*	.	0.30	0.77
Gln	84	A	A	1.21	0.01	.	*	.	-0.15	1.04
Gly	85	A	A	1.10	0.01	*	*	.	-0.30	0.61
His	86	A	A	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	0.92	-0.67	.	*	.	0.75	1.47
Ala	88	A	A	1.52	-0.39	.	*	.	0.45	1.22
Glu	89	A	A	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	-0.14	0.21	.	*	.	-0.10	0.36
Gly	96	A	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	-0.28	-0.21	.	*	F	0.65	0.71
Lys	99	A	A	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	0.66	-0.46	.	.	F	0.60	1.01

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	101	A	A	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	-0.80	0.49	*	*	.	-0.60	0.38
Thr	109	A	A	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	C	0.34	0.00	*	.	F	2.20	1.47
Ala	119	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	C	1.66	-0.60	*	.	F	1.15	0.89
Gln	136	C	1.66	-0.60	*	.	F	1.49	0.79
Gly	137	T	C	1.30	-0.60	*	.	F	2.18	1.35
Pro	138	T	C	0.84	-0.61	*	.	F	2.52	2.63
Glu	139	T	C	1.13	-0.83	*	.	F	2.86	1.50
Glu	140	T	T	.	1.74	-0.84	.	.	F	3.40	2.03
Thr	141	T	.	.	1.43	-0.51	.	.	F	2.86	2.06
Gly	142	T	T	.	1.08	-0.46	.	.	F	2.42	1.72
Ser	143	T	T	.	0.43	0.33	.	.	F	1.33	0.86
Tyr	144	T	T	.	0.22	0.97	.	.	.	0.54	0.44
Thr	145	T	T	.	-0.07	0.91	.	.	.	0.20	0.69
Phe	146	.	.	B	B	.	.	.	-0.57	1.40	.	.	.	-0.60	0.54
Val	147	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	148	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	149	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	150	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Leu	151	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ser	152	A	0.19	0.46	*	.	.	0.20	0.71
Phe	153	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	154	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	155	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly	156	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	157	A	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	158	A	A	1.66	-1.00	*	.	F	1.35	0.76
Leu	159	A	A	1.61	-1.00	.	.	F	1.20	1.54
Glu	160	A	A	1.50	-1.43	.	.	F	0.90	1.98
Glu	161	A	A	1.89	-1.41	*	.	F	0.90	3.16
Lys	162	A	A	1.30	-1.91	*	.	F	0.90	7.66
Glu	163	A	A	1.08	-1.91	.	.	F	0.90	3.10
Asn	164	A	A	1.03	-1.23	*	*	F	0.90	1.48
Lys	165	A	A	1.08	-0.59	*	.	F	0.75	0.55
Ile	166	A	A	1.08	-0.59	*	*	.	0.60	0.63
Leu	167	A	A	0.72	-0.59	*	*	.	0.76	0.68
Val	168	A	A	0.38	-0.50	.	*	.	0.92	0.49
Lys	169	A	A	0.13	-0.07	*	*	F	0.93	0.69
Glu	170	A	T	.	-0.61	0.00	*	*	F	1.64	1.32
Thr	171	T	T	.	-0.42	0.10	.	*	F	1.60	1.54
Gly	172	T	T	.	-0.50	0.24	*	.	F	1.29	0.67
Tyr	173	T	T	.	0.11	0.93	*	*	.	0.68	0.27
Phe	174	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.28	0.29
Phe	175	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.44	0.29
Ile	176	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	177	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	178	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	179	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	180	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	181	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92
Tyr	182	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	183	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	184	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	185	A	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	186	A	A	0.90	-0.16	.	.	F	0.60	1.73
Tyr	187	A	A	1.11	-0.21	.	.	.	0.45	1.03
Ala	188	A	A	0.61	0.29	.	.	.	-0.30	0.70
Met	189	A	A	-0.28	0.97	.	.	.	-0.60	0.40
Gly	190	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	191	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31
Leu	192	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	193	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln	194	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg	195	A	A	.	B	.	.	.	1.08	-0.59	*	*	F	0.90	1.62
Lys	196	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys	197	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val	198	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	199	.	A	B	B	.	.	.	0.91	0.00	*	*	.	0.30	0.29
Val	200	.	A	B	B	.	.	.	0.80	0.00	*	*	.	0.30	0.25

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Phe	201	.	.	B	B	.	.	.	-0.06	0.00	*	.	.	0.30	0.57
Gly	202	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	203	A	-0.36	-0.07	*	.	.	0.50	0.63
Glu	204	A	-1.18	-0.03	*	.	.	0.50	0.60
Leu	205	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	206	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	207	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	208	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	209	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	210	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	211	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	212	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	213	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	214	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	215	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	216	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met	217	.	.	.	B	.	.	C	0.01	0.01	*	.	F	0.20	2.44
Pro	218	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	219	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	220	C	1.36	0.04	*	.	F	1.12	1.82
Leu	221	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	222	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	223	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	224	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	225	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	226	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	227	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	228	A	-0.42	0.71	.	.	.	-0.40	0.18
Ala	229	A	A	-0.38	0.83	.	.	.	-0.60	0.34
Gly	230	A	A	-0.89	0.26	.	.	.	-0.30	0.43
Ile	231	A	A	-0.22	0.19	*	.	.	-0.30	0.27
Ala	232	A	A	0.02	-0.20	*	.	.	0.30	0.46
Lys	233	A	A	-0.02	-0.70	.	.	.	0.60	0.80
Leu	234	A	A	0.57	-0.70	.	.	F	0.90	1.13
Glu	235	A	A	0.91	-1.39	.	.	F	0.90	1.87
Glu	236	A	A	0.99	-1.89	.	.	F	0.90	1.62
Gly	237	A	A	1.58	-1.20	.	*	F	0.90	1.62
Asp	238	A	A	0.72	-1.49	.	*	F	0.90	1.62
Glu	239	A	A	0.94	-0.80	*	*	F	0.75	0.77
Leu	240	A	A	0.06	-0.30	*	*	.	0.30	0.79
Gln	241	A	A	-0.16	-0.04	*	.	.	0.30	0.33
Leu	242	A	A	0.30	0.39	*	.	.	-0.30	0.30
Ala	243	A	A	0.30	0.39	*	.	.	-0.30	0.70
Ile	244	A	A	0.30	-0.30	.	*	.	0.30	0.70
Pro	245	A	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg	246	A	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu	247	A	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn	248	A	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala	249	A	0.81	-0.63	*	*	.	0.95	1.05
Gln	250	A	1.02	0.06	*	*	.	-0.10	0.50

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ile	251	A	0.57	0.06	*	*	.	0.15	0.52
Ser	252	C	0.57	0.09	.	*	.	0.60	0.51
Leu	253	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp	254	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	255	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	256	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	257	A	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	258	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	259	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	260	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	261	A	A	-1.58	0.67	.	*	.	-0.60	0.28
Ala	262	A	A	-1.53	0.87	.	*	.	-0.60	0.27
Leu	263	A	A	-1.61	0.77	*	.	.	-0.60	0.26
Lys	264	A	A	-1.30	0.41	*	.	.	-0.60	0.33
Leu	265	A	A	-0.99	0.41	.	.	.	-0.60	0.42
Leu	266	A	A	-1.03	0.34	*	.	.	-0.30	0.65

[0083] In another embodiment, the invention provides antibodies that bind a polypeptide comprising, or alternatively consisting of, an epitope-bearing portion of a polypeptide of the invention. The epitope of this polypeptide portion may be an immunogenic or antigenic epitope of a polypeptide of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81:3998- 4002 (1983).

[0084] As to the selection of polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R. A. (1983) "Antibodies that react with predetermined sites on proteins", *Science*, 219:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals. Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. See, for instance, Wilson *et al.*, *Cell* 37:767-778 (1984) at 777.

[0085] In specific embodiments, antibodies of the present invention bind antigenic epitope-bearing peptides and polypeptides of ~~BLySB~~ Lymphocyte Stimulator and preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids contained within the amino acid sequence of a ~~BLySB~~ Lymphocyte Stimulator polypeptide. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof.

[0086] Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLySB Lymphocyte Stimulator-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-115 to about Leu-147 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-150 to about Tyr-163 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-171 to about Phe-194 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-223 to about Tyr-246 in SEQ ID NO:3228; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-271 to about Phe-278 in Figures 1A and 1B (SEQ ID NO:3228). In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLySB Lymphocyte Stimulator polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed Table 9, above.

[0087] Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLySB Lymphocyte Stimulator-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-32 to about Leu-47 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-116 to about Ser-143 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-153 to about Tyr-173 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-218 to about Tyr-227 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ala-232 to about Gln-241 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-244 to about Ala-249 in SEQ ID NO:3229; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-252 to about Val-257 in SEQ ID NO:3229. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide

fragments have been determined to bear antigenic epitopes of the BLySB Lymphocyte Stimulator polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed in Table 10 generated by the Protean component of the DNA*STAR computer program (as set forth above).

[0088] BLySB Lymphocyte Stimulator epitope-bearing peptides and polypeptides may be produced by any conventional means. *See, e.g.*, Houghten, R. A. (1985) General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids. *Proc. Natl. Acad. Sci. USA* 82:5131-5135; this "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U. S. Patent No. 4,631,211 to Houghten et al. (1986).

[0089] The present invention encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3228, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCCATCC™ deposit No. 97768, or encoded by a polynucleotide that hybridizes to cDNA sequence contained in ATCCATCC™ deposit No. 97768 (e.g., under hybridization conditions described herein).

[0090] The present invention also encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3229, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCCATCC™ deposit No. 203518, or encoded by a polynucleotide that hybridizes to the cDNA sequence contained in ATCCATCC™ deposit No. 203518 (e.g., under hybridization conditions described herein).

[0091] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses antibodies that bind a polypeptide comprising an epitope. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays

described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0092] BLySB Lymphocyte Stimulator polypeptide fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

[0093] In the present invention, antibodies of the present invention bind antigenic epitopes preferably containing a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes that may be bound by antibodies of the present invention are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0094] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes of BLySB Lymphocyte Stimulator may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be

sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0095] Epitope-bearing BLySB Lymphocyte Stimulator polypeptides may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 micrograms of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0096] As one of skill in the art will appreciate, and as discussed above, the antibodies of the present invention may bind polypeptides comprising an immunogenic or antigenic epitope fused to other polypeptide sequences. For example, the BLySB Lymphocyte Stimulator polypeptides may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has

been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix-binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni²⁺ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

[0097] In another embodiment, the antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides and/or the epitope-bearing fragments thereof that are fused with a heterologous antigen (e.g., polypeptide, carbohydrate, phospholipid, or nucleic acid). In specific embodiments, the heterologous antigen is an immunogen.

[0098] In a more specific embodiment, the heterologous antigen is the gp120 protein of HIV, or a fragment thereof.

[0099] In another embodiment, antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides and/or the epitope-bearing fragments thereof that are fused with polypeptide sequences of another TNF ligand family member (or biologically active fragments or variants thereof). In a specific embodiment, the antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides of the present

invention are fused with a CD40L polypeptide sequence. In a preferred embodiment, the CD40L polypeptide sequence is soluble.

[0100] In another embodiment, antibodies of the present invention bind mutant BLySB Lymphocyte Stimulator polypeptides that have been generated by random mutagenesis of a polynucleotide encoding the BLySB Lymphocyte Stimulator polypeptide, by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, antibodies of the present invention bind one or more components, motifs, sections, parts, domains, fragments, etc., of BLySB Lymphocyte Stimulator recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are, for example, TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190), endokine-alpha (International Publication No. WO 98/07880), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), TR12, CAD, and v-FLIP. In further embodiments, the heterologous molecules are any member of the TNF family.

[0101] In another preferred embodiment, antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides of the invention (including biologically active fragments or variants thereof), that are fused with soluble APRIL polypeptides (e.g., amino acid residues 105 through 250 of SEQ ID NO:3239), or biologically active fragments or variants thereof.

[0102] To improve or alter the characteristics of BLySB Lymphocyte Stimulator polypeptides, protein engineering may be employed. Recombinant DNA technology

known to those skilled in the art can be used to create novel mutant proteins or “muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. For instance, for many proteins, including the extracellular domain or the mature form(s) of a secreted protein, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. For instance, Ron et al., J. Biol. Chem., 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing. Accordingly, antibodies of the present invention may bind BLySB Lymphocyte Stimulator polypeptide mutants or variants generated by protein engineering.

[0103] In the present case, since the protein of the invention is a member of the TNF polypeptide family, deletions of N-terminal amino acids up to the Gly (G) residue at position 191 in SEQ ID NO:3228 may retain some biological activity such as, for example, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and cytotoxicity to appropriate target cells. Polypeptides having further N-terminal deletions including the Gly (G) residue would not be expected to retain biological activities because it is known that this residue in TNF-related polypeptides is in the beginning of the conserved domain required for biological activities. However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or extracellular domain of the protein generally will be retained when less than the majority of the residues of the complete or extracellular domain of the protein are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0104] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino

acid sequence of the BLySB Lymphocyte Stimulator of SEQ ID NO:3228, up to the glycine residue at position 191 (Gly-191 residue from the amino terminus). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n¹-285 of SEQ ID NO:3228, where n¹ is an integer in the range of the amino acid position of amino acid residues 2-190 of the amino acid sequence in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 2-285, 3-285, 4-285, 5-285, 6-285, 7-285, 8-285, 9-285, 10-285, 11-285, 12-285, 13-285, 14-285, 15-285, 16-285, 17-285, 18-285, 19-285, 20-285, 21-285, 22-285, 23-285, 24-285, 25-285, 26-285, 27-285, 28-285, 29-285, 30-285, 31-285, 32-285, 33-285, 34-285, 35-285, 36-285, 37-285, 38-285, 39-285, 40-285, 41-285, 42-285, 43-285, 44-285, 45-285, 46-285, 47-285, 48-285, 49-285, 50-285, 51-285, 52-285, 53-285, 54-285, 55-285, 56-285, 57-285, 58-285, 59-285, 60-285, 61-285, 62-285, 63-285, 64-285, 65-285, 66-285, 67-285, 68-285, 69-285, 70-285, 71-285, 72-285, 73-285, 74-285, 75-285, 76-285, 77-285, 78-285, 79-285, 80-285, 81-285, 82-285, 83-285, 84-285, 85-285, 86-285, 87-285, 88-285, 89-285, 90-285, 91-285, 92-285, 93-285, 94-285, 95-285, 96-285, 97-285, 98-285, 99-285, 100-285, 101-285, 102-285, 103-285, 104-285, 105-285, 106-285, 107-285, 108-285, 109-285, 110-285, 111-285, 112-285, 113-285, 114-285, 115-285, 116-285, 117-285, 118-285, 119-285, 120-285, 121-285, 122-285, 123-285, 124-285, 125-285, 126-285, 127-285, 128-285, 129-285, 130-285, 131-285, 132-285, 133-285, 134-285, 135-285, 136-285, 137-285, 138-285, 139-285, 140-285, 141-285, 142-285, 143-285, 144-285, 145-285, 146-285, 147-285, 148-285, 149-285, 150-285, 151-285, 152-285, 153-285, 154-285, 155-285, 156-285, 157-285, 158-285, 159-285, 160-285, 161-285, 162-285, 163-285, 164-285, 165-285, 166-285, 167-285, 168-285, 169-285, 170-285, 171-285, 172-285, 173-285, 174-285, 175-285, 176-285, 177-285, 178-285, 179-285, 180-285, 181-285, 182-285, 183-285, 184-285, 185-285, 186-285, 187-285, 188-285, 189-285, and 190-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0105] Furthermore, since the predicted extracellular domain of the BLySB Lymphocyte Stimulator polypeptides of the invention may itself elicit biological activity, deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide (spanning positions Gln-73 to Leu-285 of SEQ ID NO:3228) may retain some biological activity such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a BLySB Lymphocyte Stimulator polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0106] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLySB Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glycine residue at position number 280. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^2 -285 of SEQ ID NO:3228, where n^2 is an integer in the range of the amino acid position of amino acid residues 73-280 in SEQ ID NO:3228, and 73 is the position of the first residue from the N-terminus of the predicted extracellular domain of the BLySB Lymphocyte Stimulator polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285;

A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to

L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0107] Highly preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence least 80%, 85%, 90% identical and more preferably at least 95%, 96%, 97%, 98%, 99% or 100% identical to BLySB Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0108] Preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 90% identical to a BLySB Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 95% identical to a BLySB Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 96% identical to a BLySB Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0109] Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 97% to a BLySB Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 98% to a BLySB Lymphocyte Stimulator polypeptide having

the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 99% identical to BLySB Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0110] In specific embodiments, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, one of the following N-terminally deleted polypeptide fragments of BLySB Lymphocyte Stimulator: amino acid residues Ala-71 through Leu-285, amino acid residues Ala-81 through Leu-285, amino acid residues Leu-112 through Leu-285, amino acid residues Ala-134 through Leu-285, amino acid residues Leu-147 through Leu-285, and amino acid residues Gly-161 through Leu-285 of SEQ ID NO:3228.

[0111] Similarly, many examples of biologically functional C-terminal deletion polypeptides are known. For instance, Interferon gamma shows up to ten times higher activities by deleting 8-10 amino acid residues from the carboxy terminus of the protein (Döbeli et al., *J. Biotechnology* 7:199-216 (1988)). Since the present protein is a member of the TNF polypeptide family, deletions of C-terminal amino acids up to the leucine residue at position 284 are expected to retain most if not all biological activity such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication. Polypeptides having deletions of up to about 10 additional C-terminal residues (i.e., up to the glycine residue at position 274) also may retain some activity such as receptor binding, although such polypeptides would lack a portion of the conserved TNF domain which extends to about Leu-284 of SEQ ID NO:3228. However, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or mature protein generally will be retained when less than the majority of the residues of the complete or mature protein are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0112] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLySB Lymphocyte Stimulator polypeptide of SEQ ID NO:3228, up to the glycine residue at position 274 (Gly-274). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m¹ of the amino acid sequence in SEQ ID NO:3228, where m¹ is any integer in the range of the amino acid position of amino acid residues 274-284 in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 1-274, 1-275, 1-276, 1-277, 1-278, 1-279, 1-280, 1-281, 1-282, 1-283 and 1-284 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0113] Also provided are antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, BLySB Lymphocyte Stimulator polypeptides with one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues n¹-m¹ of SEQ ID NO:3228, where n¹ and m¹ are integers as defined above. Also included are antibodies that bind a polypeptide comprising, or alternatively consisting of, a portion of the complete BLySB Lymphocyte Stimulator amino acid sequence encoded by the deposited cDNA clone contained in ATCCATCC™ Accession No. 97768 where this portion excludes from 1 to 190 amino acids from the amino terminus or from 1 to 11 amino acids from the C-terminus of the complete amino acid sequence (or any combination of these N-terminal and C-terminal deletions) encoded by the cDNA clone in the deposited plasmid.

[0114] Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of BLySB Lymphocyte Stimulator up to the leucine residue at position 79 of SEQ ID NO:3228 may retain some biological activity, such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities.

Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3228 would not be expected to retain biological activities.

[0115] However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0116] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of BLySB Lymphocyte Stimulator polypeptide shown in SEQ ID NO:3228, up to the leucine residue at position 79 of SEQ ID NO:3228. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 73-m² of the amino acid sequence in SEQ ID NO:3228, where m² is any integer in the range of the amino acid position of amino acid residues 79 to 285 in the amino acid sequence in SEQ ID NO:3228, and residue 78 is the position of the first residue at the C-terminus of the predicted extracellular domain of the BLySB Lymphocyte Stimulator polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to Leu-285; Q-73 to L-284; Q-73 to K-283; Q-73 to L-282; Q-73 to A-281; Q-73 to G-280; Q-73 to F-279; Q-73 to F-278; Q-73 to T-277; Q-73 to V-276; Q-73 to D-275; Q-73 to G-274; Q-73 to D-273; Q-73 to L-272; Q-73 to S-271; Q-73 to I-270; Q-73 to Q-269; Q-73 to A-268; Q-73 to N-267; Q-73 to E-266; Q-73 to R-265; Q-73 to P-264; Q-73 to I-263; Q-73 to A-262; Q-73 to L-261; Q-73 to Q-260; Q-73 to L-259; Q-73 to E-258; Q-73 to D-257; Q-73 to G-256; Q-73 to E-255; Q-73 to E-254; Q-73 to L-253; Q-73 to K-252; Q-73 to A-251; Q-73 to I-250; Q-73 to G-249; Q-73 to A-248; Q-73 to

S-247; Q-73 to Y-246; Q-73 to C-245; Q-73 to S-244; Q-73 to N-243; Q-73 to N-242; Q-73 to P-241; Q-73 to L-240; Q-73 to T-239; Q-73 to E-238; Q-73 to P-237; Q-73 to M-236; Q-73 to N-235; Q-73 to Q-234; Q-73 to I-233; Q-73 to C-232; Q-73 to R-231; Q-73 to F-230; Q-73 to L-229; Q-73 to T-228; Q-73 to V-227; Q-73 to L-226; Q-73 to S-225; Q-73 to L-224; Q-73 to E-223; Q-73 to D-222; Q-73 to G-221; Q-73 to F-220; Q-73 to V-219; Q-73 to H-218; Q-73 to V-217; Q-73 to K-216; Q-73 to K-215; Q-73 to R-214; Q-73 to Q-213; Q-73 to I-212; Q-73 to L-211; Q-73 to H-210; Q-73 to G-209; Q-73 to M-208; Q-73 to A-207; Q-73 to Y-206; Q-73 to T-205; Q-73 to K-204; Q-73 to D-203; Q-73 to T-202; Q-73 to Y-201; Q-73 to L-200; Q-73 to V-199; Q-73 to Q-198; Q-73 to G-197; Q-73 to Y-196; Q-73 to I-195; Q-73 to F-194; Q-73 to F-193; Q-73 to Y-192; Q-73 to G-191; Q-73 to T-190; Q-73 to E-189; Q-73 to K-188; Q-73 to V-187; Q-73 to L-186; Q-73 to I-185; Q-73 to K-184; Q-73 to N-183; Q-73 to E-182; Q-73 to K-181; Q-73 to E-180; Q-73 to E-179; Q-73 to L-178; Q-73 to A-177; Q-73 to S-176; Q-73 to G-175; Q-73 to R-174; Q-73 to K-173; Q-73 to F-172; Q-73 to S-171; Q-73 to L-170; Q-73 to L-169; Q-73 to W-168; Q-73 to P-167; Q-73 to V-166; Q-73 to F-165; Q-73 to T-164; Q-73 to Y-163; Q-73 to S-162; Q-73 to G-161; Q-73 to K-160; Q-73 to Q-159; Q-73 to I-158; Q-73 to T-157; Q-73 to P-156; Q-73 to T-155; Q-73 to E-154; Q-73 to S-153; Q-73 to D-152; Q-73 to A-151; Q-73 to I-150; Q-73 to L-149; Q-73 to Q-148; Q-73 to L-147; Q-73 to C-146; Q-73 to D-145; Q-73 to Q-144; Q-73 to T-143; Q-73 to V-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; and Q-73 to L-79 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind ~~BLySB~~ Lymphocyte Stimulator polypeptides comprising, or

alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0117] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLySB Lymphocyte Stimulator, which may be described generally as having residues n^2 - m^2 of SEQ ID NO:3228 where n^2 and m^2 are integers as defined above.

[0118] In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLySB Lymphocyte Stimulator amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCCATCC™ accession no. 97768, where this portion excludes from 1 to about 206 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCCATCC™ accession no. 97768, or from 1 to about 206 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCCATCC™ accession no. 97768, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCCATCC™ accession no. 97768.

[0119] As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functions or biological activities may still be retained. Thus, the ability of a shortened BLySB Lymphocyte Stimulator mutein to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLySB Lymphocyte Stimulator mutein with a large number of deleted N-terminal amino acid residues may retain some

functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six BLySB Lymphocyte Stimulator amino acid residues may often evoke an immune response.

[0120] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLySB Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glycine residue at position number 280 of the sequence shown SEQ ID NO:3228 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^3 -285 of the sequence shown in SEQ ID NO:3228, where n^3 is an integer in the range of the amino acid position of amino acid residues 1 to 280 of the amino acid sequence in SEQ ID NO:3228.

[0121] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-285; D-3 to L-285; S-4 to L-285; T-5 to L-285; E-6 to L-285; R-7 to L-285; E-8 to L-285; Q-9 to L-285; S-10 to L-285; R-11 to L-285; L-12 to L-285; T-13 to L-285; S-14 to L-285; C-15 to L-285; L-16 to L-285; K-17 to L-285; K-18 to L-285; R-19 to L-285; E-20 to L-285; E-21 to L-285; M-22 to L-285; K-23 to L-285; L-24 to L-285; K-25 to L-285; E-26 to L-285; C-27 to L-285; V-28 to L-285; S-29 to L-285; I-30 to L-285; L-31 to L-285; P-32 to L-285; R-33 to L-285; K-34 to L-285; E-35 to L-285; S-36 to L-285; P-37 to L-285; S-38 to L-285; V-39 to L-285; R-40 to L-285; S-41 to L-285; S-42 to L-285; K-43 to L-285; D-44 to L-285; G-45 to L-285; K-46 to L-285; L-47 to L-285; L-48 to L-285; A-49 to L-285; A-50 to L-285; T-51 to L-285; L-52 to L-285; L-53 to L-285; L-54 to L-285; A-55 to L-285; L-56 to L-285; L-57 to L-285; S-58 to L-285; C-59 to L-285; C-60 to L-285; L-61 to L-285; T-62 to L-285; V-63 to L-285; V-64 to L-285; S-65 to L-285; F-66 to L-285; Y-67 to L-285; Q-68 to L-285; V-69 to L-285; A-70 to L-285; A-71 to L-285; L-72 to L-285; Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285;

E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270

to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0122] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activity) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLySB Lymphocyte Stimulator mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLySB Lymphocyte Stimulator mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six BLySB Lymphocyte Stimulator amino acid residues may often evoke an immune response.

[0123] Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLySB Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m³ of SEQ ID NO:3228, where m³ is an integer in the range of the amino acid position of amino acid residues 6-284 of the amino acid sequence in SEQ ID NO:3228.

[0124] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-284; M-1 to K-283; M-1 to L-282; M-1 to A-281; M-1 to

G-280; M-1 to F-279; M-1 to F-278; M-1 to T-277; M-1 to V-276; M-1 to D-275; M-1 to G-274; M-1 to D-273; M-1 to L-272; M-1 to S-271; M-1 to I-270; M-1 to Q-269; M-1 to A-268; M-1 to N-267; M-1 to E-266; M-1 to R-265; M-1 to P-264; M-1 to I-263; M-1 to A-262; M-1 to L-261; M-1 to Q-260; M-1 to L-259; M-1 to E-258; M-1 to D-257; M-1 to G-256; M-1 to E-255; M-1 to E-254; M-1 to L-253; M-1 to K-252; M-1 to A-251; M-1 to I-250; M-1 to G-249; M-1 to A-248; M-1 to S-247; M-1 to Y-246; M-1 to C-245; M-1 to S-244; M-1 to N-243; M-1 to N-242; M-1 to P-241; M-1 to L-240; M-1 to T-239; M-1 to E-238; M-1 to P-237; M-1 to M-236; M-1 to N-235; M-1 to Q-234; M-1 to I-233; M-1 to C-232; M-1 to R-231; M-1 to F-230; M-1 to L-229; M-1 to T-228; M-1 to V-227; M-1 to L-226; M-1 to S-225; M-1 to L-224; M-1 to E-223; M-1 to D-222; M-1 to G-221; M-1 to F-220; M-1 to V-219; M-1 to H-218; M-1 to V-217; M-1 to K-216; M-1 to K-215; M-1 to R-214; M-1 to Q-213; M-1 to I-212; M-1 to L-211; M-1 to H-210; M-1 to G-209; M-1 to M-208; M-1 to A-207; M-1 to Y-206; M-1 to T-205; M-1 to K-204; M-1 to D-203; M-1 to T-202; M-1 to Y-201; M-1 to L-200; M-1 to V-199; M-1 to Q-198; M-1 to G-197; M-1 to Y-196; M-1 to I-195; M-1 to F-194; M-1 to F-193; M-1 to Y-192; M-1 to G-191; M-1 to T-190; M-1 to E-189; M-1 to K-188; M-1 to V-187; M-1 to L-186; M-1 to I-185; M-1 to K-184; M-1 to N-183; M-1 to E-182; M-1 to K-181; M-1 to E-180; M-1 to E-179; M-1 to L-178; M-1 to A-177; M-1 to S-176; M-1 to G-175; M-1 to R-174; M-1 to K-173; M-1 to F-172; M-1 to S-171; M-1 to L-170; M-1 to L-169; M-1 to W-168; M-1 to P-167; M-1 to V-166; M-1 to F-165; M-1 to T-164; M-1 to Y-163; M-1 to S-162; M-1 to G-161; M-1 to K-160; M-1 to Q-159; M-1 to I-158; M-1 to T-157; M-1 to P-156; M-1 to T-155; M-1 to E-154; M-1 to S-153; M-1 to D-152; M-1 to A-151; M-1 to I-150; M-1 to L-149; M-1 to Q-148; M-1 to L-147; M-1 to C-146; M-1 to D-145; M-1 to Q-144; M-1 to T-143; M-1 to V-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to

H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0125] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLySB Lymphocyte Stimulator polypeptide, which may be described generally as having residues n^3 - m^3 of SEQ ID NO:3228, where n^3 and m^3 are integers as defined above.

[0126] Furthermore, since the predicted extracellular domain of the BLySB Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 may itself elicit functional activity (e.g., biological activity), deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide at positions Gln-73 to Leu-266 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, to stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a BLySB Lymphocyte Stimulator polypeptide results in modification or loss of one or more functional activities of the polypeptide, other functional activities may still be retained. Thus, the ability of the

shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0127] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLySB Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the glycine residue at position number 261. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n⁴-266 of SEQ ID NO:3229, where n⁴ is an integer in the range of the amino acid position of amino acid residues 73-261 of the amino acid sequence in SEQ ID NO:3229, and 261 is the position of the first residue from the N-terminus of the predicted extracellular domain BLySB Lymphocyte Stimulator polypeptide (shown in SEQ ID NO:3229).

[0128] More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150

to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0129] Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of BLySB Lymphocyte Stimulator up to the leucine residue at position 79 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. Polypeptides having further C-terminal deletions

including Leu-79 of SEQ ID NO:3229 would not be expected to retain biological activities.

[0130] However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0131] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of BLySB Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the leucine residue at position 79 of SEQ ID NO:3229. In particular, the present invention provides antibodies that bind polypeptides having the amino acid sequence of residues 73-m⁴ of the amino acid sequence in SEQ ID NO:3229, where m⁴ is any integer in the range of the amino acid position of amino acid residues 79-265 of the amino acid sequence in SEQ ID NO:3229.

[0132] More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to L-265; Q-73 to K-264; Q-73 to L-263; Q-73 to A-262; Q-73 to G-261; Q-73 to F-260; Q-73 to F-259; Q-73 to T-258; Q-73 to V-257; Q-73 to D-256; Q-73 to G-255; Q-73 to D-254; Q-73 to L-253; Q-73 to S-252; Q-73 to I-251; Q-73 to Q-250; Q-73 to A-249; Q-73 to N-248; Q-73 to E-247; Q-73 to R-246; Q-73 to P-245; Q-73 to I-244; Q-73 to A-243; Q-73 to L-242; Q-73 to Q-241; Q-73 to L-240; Q-73 to E-239; Q-73 to D-238; Q-73 to G-237; Q-73 to E-236; Q-73 to E-235; Q-73 to L-234; Q-73 to K-233; Q-73 to A-232; Q-73 to I-231; Q-73 to G-230; Q-73 to A-229; Q-73 to S-228; Q-73 to Y-227; Q-73 to C-226; Q-73 to S-225; Q-73 to N-224; Q-73 to N-223; Q-73 to P-222; Q-73 to L-221; Q-73 to T-220; Q-73 to E-219; Q-73 to P-218; Q-73 to M-217; Q-73 to N-216; Q-73 to Q-215; Q-73 to I-214;

Q-73 to C-213; Q-73 to R-212; Q-73 to F-211; Q-73 to L-210; Q-73 to T-209; Q-73 to V-208; Q-73 to L-207; Q-73 to S-206; Q-73 to L-205; Q-73 to E-204; Q-73 to D-203; Q-73 to G-202; Q-73 to F-201; Q-73 to V-200; Q-73 to H-199; Q-73 to V-198; Q-73 to K-197; Q-73 to K-196; Q-73 to R-195; Q-73 to Q-194; Q-73 to I-193; Q-73 to L-192; Q-73 to H-191; Q-73 to G-190; Q-73 to Q-7389; Q-73 to A-188; Q-73 to Y-187; Q-73 to T-186; Q-73 to K-185; Q-73 to D-184; Q-73 to T-183; Q-73 to Y-182; Q-73 to L-181; Q-73 to V-180; Q-73 to Q-179; Q-73 to G-178; Q-73 to Y-177; Q-73 to I-176; Q-73 to F-175; Q-73 to F-174; Q-73 to Y-173; Q-73 to G-172; Q-73 to T-171; Q-73 to E-170; Q-73 to K-169; Q-73 to V-168; Q-73 to L-167; Q-73 to I-166; Q-73 to K-165; Q-73 to N-164; Q-73 to E-163; Q-73 to K-162; Q-73 to E-161; Q-73 to E-160; Q-73 to L-159; Q-73 to A-158; Q-73 to S-157; Q-73 to G-156; Q-73 to R-155; Q-73 to K-154; Q-73 to F-153; Q-73 to S-152; Q-73 to L-151; Q-73 to L-150; Q-73 to W-149; Q-73 to P-148; Q-73 to V-147; Q-73 to F-146; Q-73 to T-145; Q-73 to Y-144; Q-73 to S-143; Q-73 to G-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; Q-73 to L-79; and Q-73 to S-78 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0133] The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLySB Lymphocyte Stimulator, which may be described generally as having residues

n^4 - m^4 of SEQ ID NO:3229 where n^4 and m^4 are integers as defined above.

[0134] In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLySB Lymphocyte Stimulator amino acid sequence encoded by the cDNA clone contained in the deposit having ATCCATCC™ Accession No. 203518, where this portion excludes from 1 to about 260 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCCATCC™ Accession No. 203518, or from 1 to about 187 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCCATCC™ Accession No. 203518, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA clone contained in the deposit having ATCCATCC™ Accession No. 203518.

[0135] As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of a shortened BLySB Lymphocyte Stimulator polypeptide to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLySB Lymphocyte Stimulator mutein with a large number of deleted N-terminal amino acid residues may retain functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six BLySB Lymphocyte Stimulator amino acid residues may often evoke an immune response.

[0136] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLySB Lymphocyte Stimulator polypeptide shown in SEQ ID NO:3229, up to the glycine residue at position number 261 of the sequence shown SEQ ID NO:3229 and polynucleotides encoding such polypeptides.

In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n⁵-266 of the sequence shown in SEQ ID NO:3229, where n⁵ is an integer in the range of the amino acid position of amino acid residues 1 to 261 of the amino acid sequence in SEQ ID NO:3229.

[0137] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-266; D-3 to L-266; S-4 to L-266; T-5 to L-266; E-6 to L-266; R-7 to L-266; E-8 to L-266; Q-9 to L-266; S-10 to L-266; R-11 to L-266; L-12 to L-266; T-13 to L-266; S-14 to L-266; C-15 to L-266; L-16 to L-266; K-17 to L-266; K-18 to L-266; R-19 to L-266; E-20 to L-266; E-21 to L-266; M-22 to L-266; K-23 to L-266; L-24 to L-266; K-25 to L-266; E-26 to L-266; C-27 to L-266; V-28 to L-266; S-29 to L-266; I-30 to L-266; L-31 to L-266; P-32 to L-266; R-33 to L-266; K-34 to L-266; E-35 to L-266; S-36 to L-266; P-37 to L-266; S-38 to L-266; V-39 to L-266; R-40 to L-266; S-41 to L-266; S-42 to L-266; K-43 to L-266; D-44 to L-266; G-45 to L-266; K-46 to L-266; L-47 to L-266; L-48 to L-266; A-49 to L-266; A-50 to L-266; T-51 to L-266; L-52 to L-266; L-53 to L-266; L-54 to L-266; A-55 to L-266; L-56 to L-266; L-57 to L-266; S-58 to L-266; C-59 to L-266; C-60 to L-266; L-61 to L-266; T-62 to L-266; V-63 to L-266; V-64 to L-266; S-65 to L-266; F-66 to L-266; Y-67 to L-266; Q-68 to L-266; V-69 to L-266; A-70 to L-266; A-71 to L-266; L-72 to L-266; Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266;

T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0138] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activities) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLySB Lymphocyte Stimulator mutein to induce and/or bind to antibodies which recognize the complete or mature form or the

extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLySB Lymphocyte Stimulator mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six BLySB Lymphocyte Stimulator amino acid residues may often evoke an immune response.

[0139] Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLySB Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m⁵ of SEQ ID NO:3229, where m⁵ is an integer in the range of the amino acid position of amino acid residues 6 to 265 in the amino acid sequence of SEQ ID NO:3229.

[0140] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-265; M-1 to K-264; M-1 to L-263; M-1 to A-262; M-1 to G-261; M-1 to F-260; M-1 to F-259; M-1 to T-258; M-1 to V-257; M-1 to D-256; M-1 to G-255; M-1 to D-254; M-1 to L-253; M-1 to S-252; M-1 to I-251; M-1 to Q-250; M-1 to A-249; M-1 to N-248; M-1 to E-247; M-1 to R-246; M-1 to P-245; M-1 to I-244; M-1 to A-243; M-1 to L-242; M-1 to Q-241; M-1 to L-240; M-1 to E-239; M-1 to D-238; M-1 to G-237; M-1 to E-236; M-1 to E-235; M-1 to L-234; M-1 to K-233; M-1 to A-232; M-1 to I-231; M-1 to G-230; M-1 to A-229; M-1 to S-228; M-1 to Y-227; M-1 to C-226; M-1 to S-225; M-1 to N-224; M-1 to N-223; M-1 to P-222; M-1 to L-221; M-1 to T-220; M-1 to E-219; M-1 to P-218; M-1 to M-217; M-1 to N-216; M-1 to Q-215; M-1 to I-214; M-1 to C-213; M-1 to R-212; M-1 to F-211; M-1 to L-210; M-1 to T-209; M-1 to V-208; M-1 to L-207; M-1 to S-206; M-1 to L-205; M-1 to E-204; M-1 to D-203; M-1 to G-202; M-1 to F-201; M-1 to V-200; M-1 to H-199; M-1 to V-198; M-1 to K-197; M-1 to K-196; M-1 to R-195; M-1 to Q-194; M-1 to I-193; M-1 to L-192; M-1 to H-191; M-1 to G-190; M-1 to

M-189; M-1 to A-188; M-1 to Y-187; M-1 to T-186; M-1 to K-185; M-1 to D-184; M-1 to T-183; M-1 to Y-182; M-1 to L-181; M-1 to V-180; M-1 to Q-179; M-1 to G-178; M-1 to Y-177; M-1 to I-176; M-1 to F-175; M-1 to F-174; M-1 to Y-173; M-1 to G-172; M-1 to T-171; M-1 to E-170; M-1 to K-169; M-1 to V-168; M-1 to L-167; M-1 to I-166; M-1 to K-165; M-1 to N-164; M-1 to E-163; M-1 to K-162; M-1 to E-161; M-1 to E-160; M-1 to L-159; M-1 to A-158; M-1 to S-157; M-1 to G-156; M-1 to R-155; M-1 to K-154; M-1 to F-153; M-1 to S-152; M-1 to L-151; M-1 to L-150; M-1 to W-149; M-1 to P-148; M-1 to V-147; M-1 to F-146; M-1 to T-145; M-1 to Y-144; M-1 to S-143; M-1 to G-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%,

85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0141] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLySB Lymphocyte Stimulator polypeptide, which may be described generally as having residues n^5 - m^5 of SEQ ID NO:3229, where n^5 and m^5 are integers as defined above.

[0142] In additional embodiments, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 134- m^6 of SEQ ID NO:3228, where m^6 is an integer from 140 to 285, corresponding to the position of the amino acid residue in SEQ ID NO:3228. For example, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues A-134 to Leu-285; A-134 to L-284; A-134 to K-283; A-134 to L-282; A-134 to A-281; A-134 to G-280; A-134 to F-279; A-134 to F-278; A-134 to T-277; A-134 to V-276; A-134 to D-275; A-134 to G-274; A-134 to D-273; A-134 to L-272; A-134 to S-271; A-134 to I-270; A-134 to Q-269; A-134 to A-268; A-134 to N-267; A-134 to E-266; A-134 to R-265; A-134 to P-264; A-134 to I-263; A-134 to A-262; A-134 to L-261; A-134 to Q-260; A-134 to L-259; A-134 to E-258; A-134 to D-257; A-134 to G-256; A-134 to E-255; A-134 to E-254; A-134 to L-253; A-134 to K-252; A-134 to A-251; A-134 to I-250; A-134 to G-249; A-134 to A-248; A-134 to S-247; A-134 to Y-246; A-134 to C-245; A-134 to S-244; A-134 to N-243; A-134 to N-242; A-134 to P-241; A-134 to L-240; A-134 to T-239; A-134 to E-238; A-134 to P-237; A-134 to M-236; A-134 to N-235; A-134 to Q-234; A-134 to I-233; A-134 to C-232; A-134 to R-231; A-134 to F-230; A-134 to L-229; A-134 to T-228; A-134 to V-227; A-134 to L-226; A-134 to S-225; A-134 to L-224; A-134 to E-223; A-134 to D-222; A-134 to G-221; A-134 to F-220; A-134 to V-219; A-134 to H-218; A-134 to V-217; A-134 to K-216; A-134 to K-215; A-134 to R-214; A-134 to Q-213; A-134 to I-212; A-134 to L-211; A-134 to H-210; A-134 to G-209; A-134 to M-208; A-134 to A-207; A-134 to Y-206; A-134 to T-205; A-134 to K-204; A-134 to D-203; A-134 to T-202; A-134 to Y-201; A-134 to L-200; A-134 to V-199; A-134 to Q-198; A-134 to G-197; A-134 to Y-196; A-134 to I-195; A-134 to F-194; A-134 to F-193; A-134 to Y-192; A-134 to G-191; A-134 to T-190; A-134 to E-189; A-134 to K-188; A-134 to V-187; A-134 to L-186; A-134 to I-185; A-134 to K-184; A-134 to

N-183; A-134 to E-182; A-134 to K-181; A-134 to E-180; A-134 to E-179; A-134 to L-178; A-134 to A-177; A-134 to S-176; A-134 to G-175; A-134 to R-174; A-134 to K-173; A-134 to F-172; A-134 to S-171; A-134 to L-170; A-134 to L-169; A-134 to W-168; A-134 to P-167; A-134 to V-166; A-134 to F-165; A-134 to T-164; A-134 to Y-163; A-134 to S-162; A-134 to G-161; A-134 to K-160; A-134 to Q-159; A-134 to I-158; A-134 to T-157; A-134 to P-156; A-134 to T-155; A-134 to E-154; A-134 to S-153; A-134 to D-152; A-134 to A-151; A-134 to I-150; A-134 to L-149; A-134 to Q-148; A-134 to L-147; A-134 to C-146; A-134 to D-145; A-134 to Q-144; A-134 to T-143; A-134 to V-142; A-134 to T-141; and A-134 to E-140 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0143] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-

116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121;
 V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-
 113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to
 K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-
 137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to V-142;
 S-129 to T-143; R-130 to Q-144; N-131 to D-145; K-132 to C-146; R-133 to L-147; A-
 134 to Q-148; V-135 to L-149; Q-136 to I-150; G-137 to A-151; P-138 to D-152; E-139 to
 S-153; E-140 to E-154; T-141 to T-155; V-142 to P-156; T-143 to T-157; Q-144 to I-158;
 D-145 to Q-159; C-146 to K-160; L-147 to G-161; Q-148 to S-162; L-149 to Y-163; I-150
 to T-164; A-151 to F-165; D-152 to V-166; S-153 to P-167; E-154 to W-168; T-155 to L-
 169; P-156 to L-170; T-157 to S-171; I-158 to F-172; Q-159 to K-173; K-160 to R-174;
 G-161 to G-175; S-162 to S-176; Y-163 to A-177; T-164 to L-178; F-165 to E-179; V-166
 to E-180; P-167 to K-181; W-168 to E-182; L-169 to N-183; L-170 to K-184; S-171 to I-
 185; F-172 to L-186; K-173 to V-187; R-174 to K-188; G-175 to E-189; S-176 to T-190;
 A-177 to G-191; L-178 to Y-192; E-179 to F-193; E-180 to F-194; K-181 to I-195; E-182
 to Y-196; N-183 to G-197; K-184 to Q-198; I-185 to V-199; L-186 to L-200; V-187 to Y-
 201; K-188 to T-202; E-189 to D-203; T-190 to K-204; G-191 to T-205; Y-192 to Y-206;
 F-193 to A-207; F-194 to M-208; I-195 to G-209; Y-196 to H-210; G-197 to L-211; Q-
 198 to I-212; V-199 to Q-213; L-200 to R-214; Y-201 to K-215; T-202 to K-216; D-203
 to V-217; K-204 to H-218; T-205 to V-219; Y-206 to F-220; A-207 to G-221; M-208 to
 D-222; G-209 to E-223; H-210 to L-224; L-211 to S-225; I-212 to L-226; Q-213 to V-
 227; R-214 to T-228; K-215 to L-229; K-216 to F-230; V-217 to R-231; H-218 to C-232;
 V-219 to I-233; F-220 to Q-234; G-221 to N-235; D-222 to M-236; E-223 to P-237; L-224
 to E-238; S-225 to T-239; L-226 to L-240; V-227 to P-241; T-228 to N-242; L-229 to N-
 243; F-230 to S-244; R-231 to C-245; C-232 to Y-246; I-233 to S-247; Q-234 to A-248;
 N-235 to G-249; M-236 to I-250; P-237 to A-251; E-238 to K-252; T-239 to L-253; L-240
 to E-254; P-241 to E-255; N-242 to G-256; N-243 to D-257; S-244 to E-258; C-245 to L-
 259; Y-246 to Q-260; S-247 to L-261; A-248 to A-262; G-249 to I-263; I-250 to P-264;
 A-251 to R-265; K-252 to E-266; L-253 to N-267; E-254 to A-268; E-255 to Q-269; G-
 256 to I-270; D-257 to S-271; E-258 to L-272; L-259 to D-273; Q-260 to G-274; L-261 to
 D-275; A-262 to V-276; I-263 to T-277; P-264 to F-278; R-265 to F-279; E-266 to G-280;
 N-267 to A-281; A-268 to L-282; Q-269 to K-283; I-270 to L-284; and S-271 to L-285 of

SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0144] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to G-142; S-129 to S-143; R-130 to Y-144; N-131 to T-145; K-132 to F-146; R-133 to V-147; A-134 to P-148; V-135 to W-149; Q-136 to L-150; G-137 to L-151; P-138 to S-152; E-139 to F-153; E-140 to K-154; T-141 to R-155; G-142 to G-156; S-143 to S-157; Y-144 to A-

158; T-145 to L-159; F-146 to E-160; V-147 to E-161; P-148 to K-162; W-149 to E-163; L-150 to N-164; L-151 to K-165; S-152 to I-166; F-153 to L-167; K-154 to V-168; R-155 to K-169; G-156 to E-170; S-157 to T-171; A-158 to G-172; L-159 to Y-173; E-160 to F-174; E-161 to F-175; K-162 to I-176; E-163 to Y-177; N-164 to G-178; K-165 to Q-179; I-166 to V-180; L-167 to L-181; V-168 to Y-182; K-169 to T-183; E-170 to D-184; T-171 to K-185; G-172 to T-186; Y-173 to Y-187; F-174 to A-188; F-175 to M-189; I-176 to G-190; Y-177 to H-191; G-178 to L-192; Q-179 to I-193; V-180 to Q-194; L-181 to R-195; Y-182 to K-196; T-183 to K-197; D-184 to V-198; K-185 to H-199; T-186 to V-200; Y-187 to F-201; A-188 to G-202; M-189 to D-203; G-190 to E-204; H-191 to L-205; L-192 to S-206; I-193 to L-207; Q-194 to V-208; R-195 to T-209; K-196 to L-210; K-197 to F-211; V-198 to R-212; H-199 to C-213; V-200 to I-214; F-201 to Q-215; G-202 to N-216; D-203 to M-217; E-204 to P-218; L-205 to E-219; S-206 to T-220; L-207 to L-221; V-208 to P-222; T-209 to N-223; L-210 to N-224; F-211 to S-225; R-212 to C-226; C-213 to Y-227; I-214 to S-228; Q-215 to A-229; N-216 to G-230; M-217 to I-231; P-218 to A-232; E-219 to K-233; T-220 to L-234; L-221 to E-235; P-222 to E-236; N-223 to G-237; N-224 to D-238; S-225 to E-239; C-226 to L-240; Y-227 to Q-241; S-228 to L-242; A-229 to A-243; G-230 to I-244; I-231 to P-245; A-232 to R-246; K-233 to E-247; L-234 to N-248; E-235 to A-249; E-236 to Q-250; G-237 to I-251; D-238 to S-252; E-239 to L-253; L-240 to D-254; Q-241 to G-255; L-242 to D-256; A-243 to V-257; I-244 to T-258; P-245 to F-259; R-246 to F-260; E-247 to G-261; N-248 to A-262; A-249 to L-263; Q-250 to K-264; I-251 to L-265; and S-252 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0145] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to F-15; D-2 to C-16; E-3 to S-17; S-4 to E-18; A-5 to K-19; K-6 to G-20; T-7 to E-21; L-8 to D-22; P-9 to M-23; P-10 to K-24; P-11 to V-25; C-12 to G-26; L-13 to Y-27; C-14 to D-28; F-15 to P-29; C-16 to I-30; S-17 to T-31; E-18 to P-32; K-19 to Q-33; G-20 to K-34; E-21 to E-35; D-22 to E-36; M-23 to G-37; K-24 to A-38; V-25 to W-39; G-26 to F-40; Y-27 to G-41; D-28 to I-42; P-29 to C-

43; I-30 to R-44; T-31 to D-45; P-32 to G-46; Q-33 to R-47; K-34 to L-48; E-35 to L-49;
 E-36 to A-50; G-37 to A-51; A-38 to T-52; W-39 to L-53; F-40 to L-54; G-41 to L-55; I-
 42 to A-56; C-43 to L-57; R-44 to L-58; D-45 to S-59; G-46 to S-60; R-47 to S-61; L-48
 to F-62; L-49 to T-63; A-50 to A-64; A-51 to M-65; T-52 to S-66; L-53 to L-67; L-54 to
 Y-68; L-55 to Q-69; A-56 to L-70; L-57 to A-71; L-58 to A-72; S-59 to L-73; S-60 to Q-
 74; S-61 to A-75; F-62 to D-76; T-63 to L-77; A-64 to M-78; M-65 to N-79; S-66 to L-80;
 L-67 to R-81; Y-68 to M-82; Q-69 to E-83; L-70 to L-84; A-71 to Q-85; A-72 to S-86; L-
 73 to Y-87; Q-74 to R-88; A-75 to G-89; D-76 to S-90; L-77 to A-91; M-78 to T-92; N-79
 to P-93; L-80 to A-94; R-81 to A-95; M-82 to A-96; E-83 to G-97; L-84 to A-98; Q-85 to
 P-99; S-86 to E-100; Y-87 to L-101; R-88 to T-102; G-89 to A-103; S-90 to G-104; A-91
 to V-105; T-92 to K-106; P-93 to L-107; A-94 to L-108; A-95 to T-109; A-96 to P-110;
 G-97 to A-111; A-98 to A-112; P-99 to P-113; E-100 to R-114; L-101 to P-115; T-102 to
 H-116; A-103 to N-117; G-104 to S-118; V-105 to S-119; K-106 to R-120; L-107 to G-
 121; L-108 to H-122; T-109 to R-123; P-110 to N-124; A-111 to R-125; A-112 to R-126;
 P-113 to A-127; R-114 to F-128; P-115 to Q-129; H-116 to G-130; N-117 to P-131; S-118
 to E-132; S-119 to E-133; R-120 to T-134; G-121 to E-135; H-122 to Q-136; R-123 to D-
 137; N-124 to V-138; R-125 to D-139; R-126 to L-140; A-127 to S-141; F-128 to A-142;
 Q-129 to P-143; G-130 to P-144; P-131 to A-145; E-132 to P-146; E-133 to C-147; T-134
 to L-148; E-135 to P-149; Q-136 to G-150; D-137 to C-151; V-138 to R-152; D-139 to H-
 153; L-140 to S-154; S-141 to Q-155; A-142 to H-156; P-143 to D-157; P-144 to D-158;
 A-145 to N-159; P-146 to G-160; C-147 to M-161; L-148 to N-162; P-149 to L-163; G-
 150 to R-164; C-151 to N-165; R-152 to I-166; H-153 to I-167; S-154 to Q-168; Q-155 to
 D-169; H-156 to C-170; D-157 to L-171; D-158 to Q-172; N-159 to L-173; G-160 to I-
 174; M-161 to A-175; N-162 to D-176; L-163 to S-177; R-164 to D-178; N-165 to T-179;
 I-166 to P-180; I-167 to A-181; Q-168 to L-182; D-169 to E-183; C-170 to E-184; L-171
 to K-185; Q-172 to E-186; L-173 to N-187; I-174 to K-188; A-175 to I-189; D-176 to V-
 190; S-177 to V-191; D-178 to R-192; T-179 to Q-193; P-180 to T-194; A-181 to G-195;
 L-182 to Y-196; E-183 to F-197; E-184 to F-198; K-185 to I-199; E-186 to Y-200; N-187
 to S-201; K-188 to Q-202; I-189 to V-203; V-190 to L-204; V-191 to Y-205; R-192 to T-
 206; Q-193 to D-207; T-194 to P-208; G-195 to I-209; Y-196 to F-210; F-197 to A-211;
 F-198 to M-212; I-199 to G-213; Y-200 to H-214; S-201 to V-215; Q-202 to I-216; V-203
 to Q-217; L-204 to R-218; Y-205 to K-219; T-206 to K-220; D-207 to V-221; P-208 to H-

222; I-209 to V-223; F-210 to F-224; A-211 to G-225; M-212 to D-226; G-213 to E-227; H-214 to L-228; V-215 to S-229; I-216 to L-230; Q-217 to V-231; R-218 to T-232; K-219 to L-233; K-220 to F-234; V-221 to R-235; H-222 to C-236; V-223 to I-237; F-224 to Q-238; G-225 to N-239; D-226 to M-240; E-227 to P-241; L-228 to K-242; S-229 to T-243; L-230 to L-244; V-231 to P-245; T-232 to N-246; L-233 to N-247; F-234 to S-248; R-235 to C-249; C-236 to Y-250; I-237 to S-251; Q-238 to A-252; N-239 to G-253; M-240 to I-254; P-241 to A-255; K-242 to R-256; T-243 to L-257; L-244 to E-258; P-245 to E-259; N-246 to G-260; N-247 to D-261; S-248 to E-262; C-249 to I-263; Y-250 to Q-264; S-251 to L-265; A-252 to A-266; G-253 to I-267; I-254 to P-268; A-255 to R-269; R-256 to E-270; L-257 to N-271; E-258 to A-272; E-259 to Q-273; G-260 to I-274; D-261 to S-275; E-262 to R-276; I-263 to N-277; Q-264 to G-278; L-265 to D-279; A-266 to D-280; I-267 to T-281; P-268 to F-282; R-269 to F-283; E-270 to G-284; N-271 to A-285; A-272 to L-286; Q-273 to K-287; I-274 to L-288; and S-275 to L-289 of SEQ ID NO:38. The present invention is also directed to antibodies that bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLySB Lymphocyte Stimulator polypeptides described above.

[0146] It will be recognized by one of ordinary skill in the art that some amino acid sequences of the BLySB Lymphocyte Stimulator polypeptides can be varied without significant effect of the structure or function of the polypeptide. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the polypeptide which determine activity.

[0147] Thus, the invention further includes antibodies that bind variations of BLySB Lymphocyte Stimulator polypeptides which show BLySB Lymphocyte Stimulator polypeptide functional activity (e.g., biological activity) or which include regions of BLySB Lymphocyte Stimulator polypeptide such as the polypeptide fragments described herein. Such mutants include deletions, insertions, inversions, repeats, and type substitutions selected according to general rules known in the art so as to have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1306-1310 (1990), wherein the authors indicate that there are two main approaches for studying the tolerance

of an amino acid sequence to change. The first method relies on the process of evolution, in which mutations are either accepted or rejected by natural selection. The second approach uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene and selections or screens to identify sequences that maintain functionality.

[0148] As the authors state, these studies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at a certain position of the protein. For example, most buried amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Other such phenotypically silent substitutions are described in Bowie, J. U. *et al.*, *supra*, and the references cited therein. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe, Tyr.

[0149] Thus, antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3228, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence.

[0150] Antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3229, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved

amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as, a soluble biologically active fragment of another TNF ligand family member (e.g., CD40 Ligand), an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

[0151] Thus, the antibodies of the invention may bind B_LySB Lymphocyte Stimulator polypeptides that include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation. As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 13).

[0152] TABLE 13. Conservative Amino Acid Substitutions.

[0153]	Aromatic	[0159]	Phenylalanine
		[0160]	Tryptophan
		[0161]	Tyrosine
[0154]	Hydrophobic	[0162]	Leucine
		[0163]	Isoleucine
		[0164]	Valine
[0155]	Polar	[0165]	Glutamine
		[0166]	Asparagine
[0156]	Basic	[0167]	Arginine
		[0168]	Lysine
		[0169]	Histidine
[0157]	Acidic	[0170]	Aspartic Acid
		[0171]	Glutamic Acid
[0158]	Small	[0172]	Alanine
		[0173]	Serine

	[0174]	Threonine
	[0175]	Methionine
	[0176]	Glycine

[0177] In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLySB Lymphocyte Stimulator polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 50 conservative amino acid substitutions, even more preferably, not more than 40 conservative amino acid substitutions, still more preferably, not more than 30 conservative amino acid substitutions, and still even more preferably, not more than 20 conservative amino acid substitutions. In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLySB Lymphocyte Stimulator polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 conservative amino acid substitutions.

[0178] For example, site directed changes at the amino acid level of BLySB Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLySB Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3228 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39

replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A,

I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V;
 S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q;
 S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced
 with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G,
 I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N;
 G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D;
 T141 replaced with A, G, I, L, S, M, or V; V142 replaced with A, G, I, L, S, T, or M;
 T143 replaced with A, G, I, L, S, M, or V; Q144 replaced with N; D145 replaced with E;
 L147 replaced with A, G, I, S, T, M, or V; Q148 replaced with N; L149 replaced with A,
 G, I, S, T, M, or V; I150 replaced with A, G, L, S, T, M, or V; A151 replaced with G, I, L,
 S, T, M, or V; D152 replaced with E; S153 replaced with A, G, I, L, T, M, or V; E154
 replaced with D; T155 replaced with A, G, I, L, S, M, or V; T157 replaced with A, G, I, L,
 S, M, or V; I158 replaced with A, G, L, S, T, M, or V; Q159 replaced with N; K160
 replaced with H, or R; G161 replaced with A, I, L, S, T, M, or V; S162 replaced with A,
 G, I, L, T, M, or V; Y163 replaced with F, or W; T164 replaced with A, G, I, L, S, M, or
 V; F165 replaced with W, or Y; V166 replaced with A, G, I, L, S, T, or M; W168 replaced
 with F, or Y; L169 replaced with A, G, I, S, T, M, or V; L170 replaced with A, G, I, S, T,
 M, or V; S171 replaced with A, G, I, L, T, M, or V; F172 replaced with W, or Y; K173
 replaced with H, or R; R174 replaced with H, or K; G175 replaced with A, I, L, S, T, M,
 or V; S176 replaced with A, G, I, L, T, M, or V; A177 replaced with G, I, L, S, T, M, or
 V; L178 replaced with A, G, I, S, T, M, or V; E179 replaced with D; E180 replaced with
 D; K181 replaced with H, or R; E182 replaced with D; N183 replaced with Q; K184
 replaced with H, or R; I185 replaced with A, G, L, S, T, M, or V; L186 replaced with A,
 G, I, S, T, M, or V; V187 replaced with A, G, I, L, S, T, or M; K188 replaced with H, or
 R; E189 replaced with D; T190 replaced with A, G, I, L, S, M, or V; G191 replaced with
 A, I, L, S, T, M, or V; Y192 replaced with F, or W; F193 replaced with W, or Y; F194
 replaced with W, or Y; I195 replaced with A, G, L, S, T, M, or V; Y196 replaced with F,
 or W; G197 replaced with A, I, L, S, T, M, or V; Q198 replaced with N; V199 replaced
 with A, G, I, L, S, T, or M; L200 replaced with A, G, I, S, T, M, or V; Y201 replaced with
 F, or W; T202 replaced with A, G, I, L, S, M, or V; D203 replaced with E; K204 replaced
 with H, or R; T205 replaced with A, G, I, L, S, M, or V; Y206 replaced with F, or W;
 A207 replaced with G, I, L, S, T, M, or V; M208 replaced with A, G, I, L, S, T, or V;

G209 replaced with A, I, L, S, T, M, or V; H210 replaced with K, or R; L211 replaced with A, G, I, S, T, M, or V; I212 replaced with A, G, L, S, T, M, or V; Q213 replaced with N; R214 replaced with H, or K; K215 replaced with H, or R; K216 replaced with H, or R; V217 replaced with A, G, I, L, S, T, or M; H218 replaced with K, or R; V219 replaced with A, G, I, L, S, T, or M; F220 replaced with W, or Y; G221 replaced with A, I, L, S, T, M, or V; D222 replaced with E; E223 replaced with D; L224 replaced with A, G, I, S, T, M, or V; S225 replaced with A, G, I, L, T, M, or V; L226 replaced with A, G, I, S, T, M, or V; V227 replaced with A, G, I, L, S, T, or M; T228 replaced with A, G, I, L, S, M, or V; L229 replaced with A, G, I, S, T, M, or V; F230 replaced with W, or Y; R231 replaced with H, or K; I233 replaced with A, G, L, S, T, M, or V; Q234 replaced with N; N235 replaced with Q; M236 replaced with A, G, I, L, S, T, or V; E238 replaced with D; T239 replaced with A, G, I, L, S, M, or V; L240 replaced with A, G, I, S, T, M, or V; N242 replaced with Q; N243 replaced with Q; S244 replaced with A, G, I, L, T, M, or V; Y246 replaced with F, or W; S247 replaced with A, G, I, L, T, M, or V; A248 replaced with G, I, L, S, T, M, or V; G249 replaced with A, I, L, S, T, M, or V; I250 replaced with A, G, L, S, T, M, or V; A251 replaced with G, I, L, S, T, M, or V; K252 replaced with H, or R; L253 replaced with A, G, I, S, T, M, or V; E254 replaced with D; E255 replaced with D; G256 replaced with A, I, L, S, T, M, or V; D257 replaced with E; E258 replaced with D; L259 replaced with A, G, I, S, T, M, or V; Q260 replaced with N; L261 replaced with A, G, I, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; I263 replaced with A, G, L, S, T, M, or V; R265 replaced with H, or K; E266 replaced with D; N267 replaced with Q; A268 replaced with G, I, L, S, T, M, or V; Q269 replaced with N; I270 replaced with A, G, L, S, T, M, or V; S271 replaced with A, G, I, L, T, M, or V; L272 replaced with A, G, I, S, T, M, or V; D273 replaced with E; G274 replaced with A, I, L, S, T, M, or V; D275 replaced with E; V276 replaced with A, G, I, L, S, T, or M; T277 replaced with A, G, I, L, S, M, or V; F278 replaced with W, or Y; F279 replaced with W, or Y; G280 replaced with A, I, L, S, T, M, or V; A281 replaced with G, I, L, S, T, M, or V; L282 replaced with A, G, I, S, T, M, or V; K283 replaced with H, or R; L284 replaced with A, G, I, S, T, M, or V; and/or L285 replaced with A, G, I, S, T, M, or V.

[0179] In another embodiment, site directed changes at the amino acid level of BLySB Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLySB

Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3229 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83

replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; G142 replaced with A, I, L, S, T, M, or V; S143 replaced with A, G, I, L, T, M, or V; Y144 replaced with F, or W; T145 replaced with A, G, I, L, S, M, or V; F146 replaced with W, or Y; V147 replaced with A, G, I, L, S, T, or M; W149 replaced with F, or Y; L150 replaced with A, G, I, S, T, M, or V; L151 replaced with A, G, I, S, T, M, or V; S152 replaced with A, G, I, L, T, M, or V; F153 replaced with W, or Y; K154 replaced with H, or R; R155 replaced with H, or K; G156 replaced with A, I, L, S, T, M, or V; S157 replaced with A, G, I, L, T, M, or V; A158 replaced with G, I, L, S, T, M, or V; L159 replaced with A, G, I, S, T, M, or V; E160 replaced with D; E161 replaced with D; K162 replaced with H, or R; E163 replaced with D; N164 replaced with Q; K165 replaced with H, or R; I166 replaced with A, G, L, S, T, M, or V; L167 replaced with A, G, I, S, T, M, or V; V168 replaced with A, G, I, L, S, T, or M; K169 replaced with H, or R; E170 replaced with D; T171 replaced with A, G, I, L,

S, M, or V; G172 replaced with A, I, L, S, T, M, or V; Y173 replaced with F, or W; F174 replaced with W, or Y; F175 replaced with W, or Y; I176 replaced with A, G, L, S, T, M, or V; Y177 replaced with F, or W; G178 replaced with A, I, L, S, T, M, or V; Q179 replaced with N; V180 replaced with A, G, I, L, S, T, or M; L181 replaced with A, G, I, S, T, M, or V; Y182 replaced with F, or W; T183 replaced with A, G, I, L, S, M, or V; D184 replaced with E; K185 replaced with H, or R; T186 replaced with A, G, I, L, S, M, or V; Y187 replaced with F, or W; A188 replaced with G, I, L, S, T, M, or V; M189 replaced with A, G, I, L, S, T, or V; G190 replaced with A, I, L, S, T, M, or V; H191 replaced with K, or R; L192 replaced with A, G, I, S, T, M, or V; I193 replaced with A, G, L, S, T, M, or V; Q194 replaced with N; R195 replaced with H, or K; K196 replaced with H, or R; K197 replaced with H, or R; V198 replaced with A, G, I, L, S, T, or M; H199 replaced with K, or R; V200 replaced with A, G, I, L, S, T, or M; F201 replaced with W, or Y; G202 replaced with A, I, L, S, T, M, or V; D203 replaced with E; E204 replaced with D; L205 replaced with A, G, I, S, T, M, or V; S206 replaced with A, G, I, L, T, M, or V; L207 replaced with A, G, I, S, T, M, or V; V208 replaced with A, G, I, L, S, T, or M; T209 replaced with A, G, I, L, S, M, or V; L210 replaced with A, G, I, S, T, M, or V; F211 replaced with W, or Y; R212 replaced with H, or K; I214 replaced with A, G, L, S, T, M, or V; Q215 replaced with N; N216 replaced with Q; M217 replaced with A, G, I, L, S, T, or V; E219 replaced with D; T220 replaced with A, G, I, L, S, M, or V; L221 replaced with A, G, I, S, T, M, or V; N223 replaced with Q; N224 replaced with Q; S225 replaced with A, G, I, L, T, M, or V; Y227 replaced with F, or W; S228 replaced with A, G, I, L, T, M, or V; A229 replaced with G, I, L, S, T, M, or V; G230 replaced with A, I, L, S, T, M, or V; I231 replaced with A, G, L, S, T, M, or V; A232 replaced with G, I, L, S, T, M, or V; K233 replaced with H, or R; L234 replaced with A, G, I, S, T, M, or V; E235 replaced with D; E236 replaced with D; G237 replaced with A, I, L, S, T, M, or V; D238 replaced with E; E239 replaced with D; L240 replaced with A, G, I, S, T, M, or V; Q241 replaced with N; L242 replaced with A, G, I, S, T, M, or V; A243 replaced with G, I, L, S, T, M, or V; I244 replaced with A, G, L, S, T, M, or V; R246 replaced with H, or K; E247 replaced with D; N248 replaced with Q; A249 replaced with G, I, L, S, T, M, or V; Q250 replaced with N; I251 replaced with A, G, L, S, T, M, or V; S252 replaced with A, G, I, L, T, M, or V; L253 replaced with A, G, I, S, T, M, or V; D254 replaced with E; G255 replaced with A, I, L, S, T, M, or V; D256 replaced with E; V257 replaced with A, G, I, L, S, T, or M;

T258 replaced with A, G, I, L, S, M, or V; F259 replaced with W, or Y; F260 replaced with W, or Y; G261 replaced with A, I, L, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; L263 replaced with A, G, I, S, T, M, or V; K264 replaced with H, or R; L265 replaced with A, G, I, S, T, M, or V; and/or L266 replaced with A, G, I, S, T, M, or V.

[0180] In another embodiment, site directed changes at the amino acid level of BLySB Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLySB Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

[0181] Amino acids in the BLySB Lymphocyte Stimulator polypeptides that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for functional activity, such ligand binding and the ability to stimulate lymphocyte (e.g., B cell) as, for example, proliferation, differentiation, and/or activation. Accordingly, antibodies of the present invention may bind amino acids in the BLySB Lymphocyte Stimulator polypeptides that are essential for function. In preferred embodiments, antibodies of the present invention bind amino acids in the BLySB Lymphocyte Stimulator polypeptides that are essential for function and inhibit BLySB Lymphocyte Stimulator polypeptide function. In other preferred embodiments, antibodies of the present invention bind amino acids in the BLySB Lymphocyte Stimulator polypeptides that are essential for function and enhance BLySB Lymphocyte Stimulator polypeptide function.

[0182] Of special interest are substitutions of charged amino acids with other charged or neutral amino acids which may produce proteins with highly desirable improved characteristics, such as less aggregation. Aggregation may not only reduce activity but also be problematic when preparing pharmaceutical formulations, because aggregates can be immunogenic (Pinckard *et al.*, *Clin. Exp. Immunol.* 2:331-340 (1967); Robbins *et al.*, *Diabetes* 36: 838-845 (1987); Cleland *et al.*, *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993).

[0183] In another embodiment, the invention provides for antibodies that bind polypeptides having amino acid sequences containing non-conservative substitutions of

the amino acid sequence provided in SEQ ID NO:3228. For example, non-conservative substitutions of the ~~BLySB~~ Lymphocyte Stimulator protein sequence provided in SEQ ID NO:3228 include: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41

replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q73 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G74 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D75 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S78 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R80 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A81 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L83 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q84 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H86 replaced with D, E, A, G, I, L, S, T, M, V, N,

Q, F, W, Y, P, or C; H87 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E89 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L91 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A93 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G94 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A95 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G96 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A97 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P98 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K99 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A107 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F115 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; G121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E122 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q127 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N128 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

C; R130 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N131 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K132 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R133 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A134 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P138 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E139 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T143 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q144 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D145 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C146 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L147 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L149 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D152 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S153 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E154 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T155 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P156 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; T157 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I158 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q159 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K160 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G161 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S162 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y163 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T164 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F165 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P167 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W168 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L169 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L170 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F172 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M,

V, P, or C; K173 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R174 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G175 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A177 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E179 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E180 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K181 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E182 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N183 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K184 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I185 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L186 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V187 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K188 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E189 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G191 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y192 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F193 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F194 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I195 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y196 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G197 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q198 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V199 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T202 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K204 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y206 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A207 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G209 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H210 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L211 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I212 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R214 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K215 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K216

replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H218 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V219 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F220 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D222 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E223 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L224 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L226 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V227 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F230 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R231 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C232 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; I233 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q234 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N235 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M236 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P237 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T239 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; N242 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N243 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y246 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S247 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A248 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I250 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K252 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E255 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G256 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D257 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E258 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y,

P, or C; L259 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q260 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I263 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P264 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R265 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E266 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N267 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A268 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q269 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I270 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S271 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L272 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D273 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G274 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D275 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V276 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T277 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F278 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F279 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G280 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A281 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L282 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K283 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L284 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L285 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

[0184] In an additional embodiment, antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, a BLySB Lymphocyte Stimulator amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

[0185] In another embodiment of the invention, antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides with non-conservative substitutions of the sequence provided in SEQ ID NO:3229 including: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7

replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q73 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G74 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D75 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S78 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R80 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A81 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L83 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q84 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H86 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H87 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E89 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L91 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A93 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G94 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A95 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G96 replaced with D,

E, H, K, R, N, Q, F, W, Y, P, or C; A97 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P98 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K99 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A107 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F115 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; G121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E122 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q127 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N128 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R130 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N131 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K132 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R133 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A134 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P138 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;

E139 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S143 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y144 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T145 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F146 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V147 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W149 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S152 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F153 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K154 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R155 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G156 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S157 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A158 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L159 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E160 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E161 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K162 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E163 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N164 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K165 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L167 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V168 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K169 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E170 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G172 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y173 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F174 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F175 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y177 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q179 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V180 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L181 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y182 replaced

with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T183 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D184 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K185 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T186 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y187 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A188 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M189 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H191 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L192 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I193 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q194 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R195 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K196 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K197 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V198 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H199 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G202 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E204 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S206 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L207 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T209 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L210 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F211 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R212 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; I214 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q215 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N216 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P218 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E219 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T220 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P222 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; N223 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N224 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or

C; S225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C226 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y227 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G230 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I231 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A232 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K233 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L234 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E235 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E236 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G237 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E239 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L242 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A243 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R246 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E247 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N248 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q250 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S252 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G255 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D256 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V257 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T258 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F259 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F260 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L263 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K264 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L265 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L266 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

[0186] In another embodiment, site directed changes at the amino acid level of

BLySB Lymphocyte Stimulator can be made by replacing a particular amino acid with a non-conservative substitution. Antibodies of the present invention may bind BLySB Lymphocyte Stimulator amino acid sequences containing non-conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

[0187] In an additional embodiment, antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, a BLySB Lymphocyte Stimulator amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

[0188] Replacement of amino acids can also change the selectivity of the binding of a ligand to cell surface receptors. For example, Ostade *et al.*, *Nature* 361:266-268 (1993) describes certain mutations resulting in selective binding of TNF-alpha to only one of the two known types of TNF receptors. Since BLySB Lymphocyte Stimulator is a member of the TNF polypeptide family, mutations similar to those in TNF-alpha are likely to have similar effects in BLySB Lymphocyte Stimulator polypeptides.

[0189] Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol.* 224:899-904 (1992) and de Vos *et al. Science* 255:306-312 (1992)).

[0190] Since BLySB Lymphocyte Stimulator is a member of the TNF-related protein family, mutations may be made in sequences encoding amino acids in the TNF conserved domain, e.g., in positions Gly-191 through Leu-284 of SEQ ID NO:3228 or in positions Gly-172 through Leu-265 of SEQ ID NO:3229, may modulate rather than completely eliminate functional activities (e.g., biological activities) of BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof. Accordingly, antibodies of the present invention may bind BLySB Lymphocyte Stimulator polypeptides that have mutations in the TNF conserved domain. In preferred embodiments, antibodies of the present invention may bind BLySB Lymphocyte Stimulator polypeptides that have mutations in the TNF conserved domain and act as antagonists of BLySB Lymphocyte Stimulator. In other preferred embodiments, antibodies of the present invention may bind BLySB Lymphocyte Stimulator polypeptides that have mutations in the TNF conserved domain and act as agonists of BLySB Lymphocyte Stimulator.

[0191] Recombinant DNA technology known to those skilled in the art (see, for instance, DNA shuffling *supra*) can be used to create novel mutant proteins or muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions.

[0192] Thus, the invention also encompasses antibodies that bind BLySB Lymphocyte Stimulator derivatives and analogs that have one or more amino acid residues deleted, added, or substituted to generate BLySB Lymphocyte Stimulator polypeptides, e.g., that are better suited for expression, scale up, etc., in the host cells. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges; N-linked glycosylation sites can be altered or eliminated to achieve, for example, expression of a homogeneous product that is more easily recovered and purified from yeast hosts which are known to hyperglycosylate N-linked sites. To this end, a variety of amino acid substitutions at one or both of the first or third amino acid positions on any one or more of the glycosylation recognition sequences in the BLySB Lymphocyte Stimulator polypeptides of the invention, and/or an amino acid deletion at the second position of any one or more such recognition sequences will prevent glycosylation of the BLySB Lymphocyte Stimulator at the modified tripeptide sequence (see, e.g., Miyajimo et al., EMBO J 5(6):1193-1197). By way of non-limiting example, mutation of the serine at position 244 to alanine either singly or in combination with mutation of the asparagine at position 242 to glutamine abolishes glycosylation of the mature soluble form of BLySB Lymphocyte Stimulator (e.g., amino acids 134-285 of SEQ ID NO:3228) when expressed in the yeast *Pichia pastoris*. A mutant BLySB Lymphocyte Stimulator polypeptide in which only the asparagine at position 242 is mutated to glutamine, is still glycosylated when expressed in *Pichia pastoris*. In this mutant, the glycosylation event may be due to the activation or unmasking of an O-linked glycosylation site at serine 244. Similar mutations affecting glycosylation could also be made in the BLySB Lymphocyte Stimulator polypeptide of SEQ ID NO:3229, i.e., asparagine-223 to glutamine and/or serine-224 to alanine of SEQ ID NO:3229. Additionally, one or more of the amino acid residues of the polypeptides of the invention (e.g., arginine and lysine residues) may be

deleted or substituted with another residue to eliminate undesired processing by proteases such as, for example, furins or kexins. One possible result of such a mutation is that BLySB Lymphocyte Stimulator polypeptide of the invention is not cleaved and released from the cell surface. Accordingly, antibodies of the invention may bind BLySB Lymphocyte Stimulator derivatives and analogs that have one or more amino acid residues deleted, added, or substituted. In other embodiments, antibodies of the invention may bind BLySB Lymphocyte Stimulator derivatives, variants or analogs that are unable to be cleaved from the cell surface.

[0193] In a specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Lys-132 and/or Arg-133 of the BLySB Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, to prevent or diminish release of the soluble form of BLySB Lymphocyte Stimulator from cells expressing BLySB Lymphocyte Stimulator. In a more specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Lys-132 of the BLySB Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to Ala-132. In another, nonexclusive specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Arg-133 of the BLySB Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to Ala-133. These mutated proteins, and/or have uses such as, for example, in ex vivo therapy or gene therapy, to engineer cells expressing a BLySB Lymphocyte Stimulator polypeptide that is retained on the surface of the engineered cells.

[0194] In a specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Cys-146 of the BLySB Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLySB Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Cys-146 is replaced with a serine amino acid residue.

[0195] In another specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Cys-232 of the BLySB Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the

mutant BLySB Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Cys-232 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

[0196] In yet another specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Cys-245 of the BLySB Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLySB Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides in which Cys-245 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

[0197] The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of the BLySB Lymphocyte Stimulator polypeptides can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988).

[0198] The antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides including the complete polypeptide encoded by the deposited cDNA (ATCCATCC™ Deposit No. 97768) including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA, the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3228, the mature soluble polypeptide of SEQ ID NO:3228, e.g., amino acids 134-285 of SEQ ID NO:3228, the extracellular domain of SEQ ID NO:3228, amino acid residues 73-285 of SEQ ID NO:3228 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0199] The antibodies of the present invention bind BLySB Lymphocyte Stimulator polypeptides including the complete polypeptide encoded by the deposited

cDNA including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA (ATCCATCC™ Deposit No. 203518), the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3229, the mature soluble of SEQ ID NO:3229, e.g., amino acid residues 134-266 of SEQ ID NO:3229, the extracellular domain of SEQ ID NO:3229, e.g., amino acid residues 73-266 of SEQ ID NO:3229 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0200] Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCCATCC™ Deposit No. 97768) or to the polypeptide of SEQ ID NO:3228, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

[0201] Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCCATCC™ Deposit No. 203518) or to the polypeptide of SEQ ID NO:3229, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0202] By "% similarity" for two polypeptides is intended a similarity score produced by comparing the amino acid sequences of the two polypeptides using the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711) and the default settings for determining similarity. Bestfit uses the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2:482-489, 1981) to find the best segment of similarity between two sequences.

[0203] By a polypeptide having an amino acid sequence at least, for example, 95%

"identical" to a reference amino acid sequence of a BLySB Lymphocyte Stimulator polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of the BLySB Lymphocyte Stimulator polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0204] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of SEQ ID NO:3228, the amino acid sequence encoded by the deposited cDNA clone HNEDU15 (ATCCATCCTM Accession No. 97768), or fragments thereof, or, for instance, to the amino acid sequence of SEQ ID NO:3229, the amino acid sequence encoded by the deposited cDNA clone HDPMC52 (ATCCATCCTM Accession No. 203518), or fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

[0205] In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred

parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue

positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

[0206] Antibodies that Immunospecifically bind BLySB Lymphocyte Stimulator Polypeptides

[0207] The present invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator polypeptides, which antibodies comprise, or alternatively consist of, all or a portion of a heavy and/or light chain variable domain of the scFvs referred to in Table 1.

[0208] The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor expression or inappropriate BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0209] The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor expression or inappropriate BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator. Diseases and

disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0210] Anti-BLySB Lymphocyte Stimulator Antibodies

[0211] The antibodies of the present invention were discovered, in part, using phage display technology. Single chain antibody molecules ("scFvs") displayed on the surface of phage particles were screened to identify those scFvs that immunospecifically bind to BLySB Lymphocyte Stimulator, including the membrane-bound form and soluble form of BLySB Lymphocyte Stimulator. The present invention encompasses the scFvs and portions thereof that were identified to immunospecifically bind to BLySB Lymphocyte Stimulator, including scFvs that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, scFvs that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator, and scFvs that immunospecifically bind to both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator. In particular, the present invention encompasses scFvs comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NOS: 1 - 2128, as referred to in Table 1. Preferably, the scFvs of the present invention comprise, or alternatively consist of, the amino acid sequence of SEQ ID NOS: 1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908. The scFvs include scFvs that bind to soluble BLySB Lymphocyte Stimulator (*e.g.*, scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1880), scFvs that bind to the membrane-bound form of BLySB Lymphocyte Stimulator (*e.g.*, scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128), and scFvs that bind to both the soluble form and the membrane-bound form of BLySB Lymphocyte Stimulator (*e.g.*, scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562). Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLySB Lymphocyte Stimulator are also encompassed by the

invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0212] In one embodiment of the present invention, scFvs that immunospecifically bind to BLySB Lymphocyte Stimulator comprise a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1 and/or any one of the VL domains referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1 and/or any one, two, three, or more of the VL CDRs referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, antibody fragments or variants of the scFvs referred to in Table 1 that immunospecifically bind to BLySB Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0213] (Table 1 can be found at the end of the specification just prior to the claims.)

[0214] In another embodiment of the present invention, an scFv that immunospecifically binds to a soluble form of BLySB Lymphocyte Stimulator, comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563 – 1880 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a soluble form of BLySB Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1570 - 1595. In an even more preferred embodiment, an scFv that immunospecifically binds to a soluble form of BLySB

Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563 - 1569.

[0215] In another embodiment of the present invention, an scFv that immunospecifically binds to a membrane-bound form of BLySB Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881 - 2128 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of BLySB Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1886 - 1908. In an even more preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of BLySB Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881 - 1885.

[0216] In another embodiment of the present invention, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1 - 1562 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:834 - 872. In another preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator comprises, or alternatively consists of, any one of the amino acids sequences of SEQ ID NOS:1 – 46 or 321 - 329. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator and/or the membrane-bound form of BLySB Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0217] In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1563 – 1880 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid

sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs SEQ ID NOS:1563 - 1880 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in contained SEQ ID NOS:1563 - 1880, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the of the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLySB Lymphocyte Stimulator, preferably the soluble form of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0218] In another embodiment of the present invention, scFvs that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator

comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting

of, fragments or variants of these scFvs, that immunospecifically bind to BLySB Lymphocyte Stimulator, preferably the membrane-bound form of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0219] In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS:1 - 1562, as disclosed

in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs or molecules, that immunospecifically bind to BLySB Lymphocyte Stimulator, preferably the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0220] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLySB Lymphocyte Stimulator. In particular, the invention provides antibodies corresponding to the scFvs referred to in Table 1, such scFvs may routinely be “converted” to immunoglobulin molecules by inserting, for example, the nucleotide sequences encoding the VH and/or VL domains of the scFv into an expression vector containing the constant domain sequences and engineered to direct the expression of the immunoglobulin molecule, as described in more detail in Example 20, *infra*.

[0221] In one embodiment, the invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one of the VH domains contained in the sequences referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide, or polypeptide fragment of BLySB Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VH CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that immunospecifically bind to BLySB Lymphocyte Stimulator or a BLySB Lymphocyte Stimulator fragment are also

encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants.

[0222] In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind BLySB Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR referred to in Table 1. In particular, the invention provides antibodies that immunospecifically bind BLySB Lymphocyte Stimulator, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind BLySB Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR2 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind BLySB Lymphocyte Stimulator, comprise, or alternatively consist of a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind BLySB Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1; a VH CDR2 contained in SEQ ID NOS: SEQ ID NOS: SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908; and/or a VH CDR3 contained in SEQ ID NOS: SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VH CDRs that are derived from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to BLySB Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0223] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide, or polypeptide fragment of BLySB

Lymphocyte Stimulator. In particular, the invention provides antibodies wherein said antibodies comprise, or alternatively consist of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of BLySB Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VL CDR having an amino acid sequence of any one, two, three, or more of the VL CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to BLySB Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0224] In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind BLySB Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR referred to in Table 1. In particular, the invention provides antibodies that immunospecifically bind BLySB Lymphocyte Stimulator, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VL CDR1 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind BLySB Lymphocyte Stimulator comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR2 contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1. In a preferred embodiment, antibodies comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS: in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 disclosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind BLySB Lymphocyte Stimulator comprise, or alternatively consist of: a polypeptide having the amino acid sequence of a VL CDR1 contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1; a VL CDR2 SEQ ID NOS :834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1; and a VL CDR3 contained SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908 as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VL CDRs that are derived

from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLySB Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0225] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLySB Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VH domain of one of the scFvs referred to in Table 1 combined with a VL domain of one of the scFvs referred to in Table 1, or other VL domain. The present invention further provides antibodies (including molecules comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLySB Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VL domain of one of the scFvs referred to in Table 1 combined with a VH domain of one of the scFvs referred to in Table 1, or other VH domain. In a preferred embodiment, antibodies that immunospecifically bind to a polypeptide or a polypeptide fragment of BLySB Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1 and a VL domain contained in contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1. In a further preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a VH and a VL domain from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLySB Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0226] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide or polypeptide fragment of BLySB Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, one, two, three, or more VH CDRs and one, two, three or more VL CDRs, as referred to in Table 1. In

particular, the invention provides for antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of BLySB Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VH CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof, of the VH CDRs and VL CDRs referred to in Table 1. In a preferred embodiment, one or more of these combinations are from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLySB Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0227] In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1, 2, or 3) and VL CDRY (where Y= 1, 2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLySB Lymphocyte Stimulator, from scFvs that bind membrane-bound BLySB Lymphocyte Stimulator, or from scFvs that bind both soluble and membrane-bound BLySB Lymphocyte Stimulator). Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to BLySB Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

[0228] The term “antibody,” as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term “antibody” encompasses not only whole antibody molecules, but also antibody fragments, as well as variants (including derivatives) of antibodies and antibody fragments. Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, single chain Fvs (scFvs), Fab fragments, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY),

class (e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁ and IgA₂) or subclass of immunoglobulin molecule. The antibodies of the present invention also include molecules comprising, or alternatively consisting of, a polypeptide having an amino acid sequence of a portion of an amino acid sequence contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908. Preferably, an antibody of the invention comprises, or alternatively consists of, a polypeptide having an amino acid sequence of a VH domain, VH CDR, VL domain, or VL CDR of any one those contained in the sequences referred to in Table 1. Antibodies of the invention also include molecules comprising, or alternatively consisting of, fragments or variants of the above antibodies that immunospecifically bind BLySB Lymphocyte Stimulator.

[0229] Most preferably the antibodies of the present invention are whole antibodies or antibody fragments that immunospecifically bind human BLySB Lymphocyte Stimulator. Antibody fragments of the invention that immunospecifically bind human BLySB Lymphocyte Stimulator include, but are not limited to, Fab, Fab' and F(ab')₂, Fd fragments, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFvs), fragments comprising, or alternatively consisting of, either a VL or VH domain, and epitope binding fragments of any of the above.

[0230] BLySB Lymphocyte Stimulator-binding antibody fragments, including single-chain antibodies, may comprise, or alternatively consist of, the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. In a preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a polypeptide that immunospecifically binds to BLySB Lymphocyte Stimulator, said polypeptides comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs referred to in Table 1, preferably a polypeptide having an amino acid sequence of a VH CDR3 and/or a VL CDR3 of contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1. Most preferably, antibodies of the invention comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs from the same scFv, as referred to in Table 1. The antibodies of the invention may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken. Most preferably, the antibodies are human antibodies. As used herein, "human" antibodies

include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries and xenomice or other organisms that have been genetically engineered to produce human antibodies. For a detailed discussion of a few of the technologies for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598; and Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995), which are incorporated by reference herein in their entirety. Human antibodies or "humanized" chimeric monoclonal antibodies can be produced using techniques described herein or otherwise known in the art. For example, methods for producing chimeric antibodies are known in the art. See, for review the following references which are hereby incorporated in their entirety: Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., *Nature* 312:643 (1984); Neuberger et al., *Nature* 314:268 (1985). In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0231] The antibodies of the present invention may be monovalent, bivalent, trivalent or multivalent. For example, monovalent scFvs can be multimerized either chemically or by association with another protein or substance. An scFv that is fused to a hexahistidine tag or a Flag tag can be multimerized using Ni-NTA agarose (Qiagen) or using anti-Flag antibodies (Stratagene, Inc.).

[0232] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a BLySB Lymphocyte Stimulator polypeptide, or fragment thereof, or may be specific for both a BLySB Lymphocyte Stimulator polypeptide, or fragment thereof, and a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., *J. Immunol.* 147:60-69 (1991); U.S. Patent Nos. 4,474,893;

4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny *et al.*, J. Immunol. 148:1547-1553 (1992).

[0233] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may bind immunospecifically to murine BLySB Lymphocyte Stimulator (e.g., a polypeptide having the amino acid sequence of human BLySB Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or BLySB Lymphocyte Stimulator expressed on human monocytes; murine BLySB Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or BLySB Lymphocyte Stimulator expressed on murine monocytes; rat BLySB Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey BLySB Lymphocyte Stimulator (e.g., the monkey BLySB Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLySB Lymphocyte Stimulator, or BLySB Lymphocyte Stimulator expressed on monkey monocytes), preferably the antibodies of the invention bind immunospecifically to human BLySB Lymphocyte Stimulator. Preferably, the antibodies of the invention bind immunospecifically to human and monkey BLySB Lymphocyte Stimulator. Also preferably, the antibodies of the invention bind immunospecifically to human BLySB Lymphocyte Stimulator and murine BLySB Lymphocyte Stimulator. More preferably, antibodies of the invention, bind immunospecifically and with higher affinity to human BLySB Lymphocyte Stimulator than to murine BLySB Lymphocyte Stimulator.

[0234] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, antibodies of the present invention cross react with APRIL (SEQ ID NO:3239; GenBank Accession No. AF046888; J. Exp. Med. 188(6):1185-1190; PCT International Publication WO97/33902). In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes

thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under hybridization conditions (as described herein).

[0235] In preferred embodiments, the antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), immunospecifically bind to BLySB Lymphocyte Stimulator and do not cross-react with any other antigens. In more preferred embodiments, the antibodies of the invention immunospecifically bind to BLySB Lymphocyte Stimulator and do not cross-react with TRAIL, APRIL, Endokine-alpha, TNF-alpha, TNF-beta, Fas-L or LIGHT.

[0236] The present invention also provides for a nucleic acid molecule, generally

[0237] isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). In one embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1 having an amino acid sequence of any one of the VH CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR2 having an amino acid sequence of any one of the VH CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR3 having an amino acid sequence of any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding antibodies that immunospecifically bind BLySB Lymphocyte Stimulator and comprise, or alternatively

consist of, fragments or variants of the VH domains and/or VH CDRs are also encompassed by the invention.

[0238] In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR1 having amino acid sequence of any one of the VL CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR2 having an amino acid sequence of any one of the VL CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR3 having an amino acid sequence of any one of the VL CDR3s referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind ~~BLySB~~ Lymphocyte Stimulator and comprise, or alternatively consist of, fragments or variants of the VL domains and/or VLCDR(s) are also encompassed by the invention.

[0239] In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1 and a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind ~~BLySB~~ Lymphocyte Stimulator and comprise, or alternatively consist of, fragments or variants of the VL and/or domains and/or VHCDR(s) and/or VLCDR(s) are also encompassed by the invention.

[0240] The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the VH domains, VH CDRs, VL domains, and VL CDRs described herein, which antibodies immunospecifically bind

to BLySB Lymphocyte Stimulator. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. In specific embodiments, the variants encode substitutions of VHCDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (*e.g.*, the ability to bind BLySB Lymphocyte Stimulator). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (*e.g.*, ability to immunospecifically bind BLySB Lymphocyte Stimulator) can be determined using techniques described herein or by routinely modifying techniques known in the art.

[0241] The antibodies of the invention include derivatives (*i.e.*, variants) that are modified, *e.g.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not affect the ability of the antibody to immunospecifically

bind to BLySB Lymphocyte Stimulator. For example, but not by way of limitation, derivatives of the invention include antibodies that have been modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[0242] In a specific embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds BLySB Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH or VL domains referred to in Table 1 under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds. , 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). In another embodiment, an antibody of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDRs or VL CDRs referred to in Table 1 under stringent conditions, *e.g.*, hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. In another embodiment, an antibody of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDR3s referred to in Table 1 under stringent conditions *e.g.*, hybridization under

conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0243] In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to BLySB Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0244] In another embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to BLySB Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or

at least 99% identical, to any one of the VL CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0245] Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be described or specified in terms of their binding affinity for to BLySB Lymphocyte Stimulator polypeptides or fragments or variants of BLySB Lymphocyte Stimulator polypeptides (e.g., to the soluble form of BLySB Lymphocyte Stimulator and/or membrane-bound form of BLySB Lymphocyte Stimulator). In specific embodiments, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides, or fragments or variants thereof, with a dissociation constant or K_D of less than or equal to 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, or 10^{-5} M. More preferably, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, or 10^{-8} M. Even more preferably, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. The invention encompasses antibodies that bind BLySB Lymphocyte Stimulator polypeptides with a dissociation constant or K_D that is within any one of the ranges that are between each of the individual recited values.

[0246] In specific embodiments, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof with an off rate (k_{off}) of less than or equal to $5 \times 10^{-2} \text{ sec}^{-1}$, 10^{-2} sec^{-1} , $5 \times 10^{-3} \text{ sec}^{-1}$ or 10^{-3} sec^{-1} . More preferably, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof with an off rate (k_{off}) less than or equal to $5 \times 10^{-4} \text{ sec}^{-1}$, 10^{-4} sec^{-1} , $5 \times 10^{-5} \text{ sec}^{-1}$, or 10^{-5} sec^{-1} $5 \times 10^{-6} \text{ sec}^{-1}$, 10^{-6} sec^{-1} , $5 \times 10^{-7} \text{ sec}^{-1}$ or 10^{-7} sec^{-1} .

The invention encompasses antibodies that bind BLySB Lymphocyte Stimulator polypeptides with an off rate (k_{off}) that is within any one of the ranges that are between each of the individual recited values.

[0247] In other embodiments, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof with an on rate (k_{on}) of greater than or equal to $10^3 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$, $10^4 \text{ M}^{-1} \text{ sec}^{-1}$ or $5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$. More preferably, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof with an on rate (k_{on}) greater than or equal to $10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $10^6 \text{ M}^{-1} \text{ sec}^{-1}$, or $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ or $10^7 \text{ M}^{-1} \text{ sec}^{-1}$. The invention encompasses antibodies that bind BLySB Lymphocyte Stimulator polypeptides with on rate (k_{on}) that is within any one of the ranges that are between each of the individual recited values.

[0248] The invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that have one or more of the same biological characteristics as one or more of the antibodies described herein. By “biological characteristics” is meant, the in vitro or in vivo activities or properties of the antibodies, such as, for example, the ability to bind to BLySB Lymphocyte Stimulator (e.g., the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator), and/or an antigenic and/or epitope region of BLySB Lymphocyte Stimulator), the ability to substantially block BLySB Lymphocyte Stimulator/BLySB Lymphocyte Stimulator receptor (e.g., TACI - GenBank accession number AAC51790 and/or BCMA - GenBank accession number NP_001183) binding, or the ability to block BLySB Lymphocyte Stimulator mediated biological activity (e.g., stimulation of B cell proliferation and immunoglobulin production). Optionally, the antibodies of the invention will bind to the same epitope as at least one of the antibodies specifically referred to herein. Such epitope binding can be routinely determined using assays known in the art.

[0249] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that neutralize BLySB Lymphocyte Stimulator or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (*i.e.*, a VH domain, VL domain, VH

CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv referred to in Table 1, more preferably having an amino acid sequence contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908, and even more preferably having an amino acid sequence contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 as disclosed in Table 1, or a fragment or variant thereof. By an antibody that “neutralizes BLySB Lymphocyte Stimulator or a fragment thereof” is meant an antibody that diminishes or abolishes the ability of BLySB Lymphocyte Stimulator to bind to its receptor (e.g., TACI and BCMA) to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the BLySB Lymphocyte Stimulator receptor signalling cascade. In one embodiment, an antibody that neutralizes BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that neutralizes BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that neutralizes BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3

contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0250] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) BLySB Lymphocyte Stimulator mediated B cell proliferation as determined by any method known in the art such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, 1886 - 1908, and even more preferably having an amino acid sequence SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits BLySB Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits BLySB Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits BLySB Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits BLySB Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0251] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that

enhance the activity of BLySB Lymphocyte Stimulator or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (*i.e.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908, and preferably having an amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885, as disclosed in Table 1, or a fragment or variant thereof. By an antibody that “enhances the activity of BLySB Lymphocyte Stimulator or a fragment thereof” is meant an antibody increases the ability of BLySB Lymphocyte Stimulator to bind to its receptor (e.g., TACI or BCMA), to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the BLySB Lymphocyte Stimulator receptor signalling cascade. In one embodiment, an antibody that enhances the activity of BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that enhances the activity of BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that enhances the

activity of BLySB Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0252] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that stimulate BLySB Lymphocyte Stimulator mediated B cell proliferation as determined by any method known in the art, such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence of SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 - 1908, and even more preferably having an amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that stimulates BLySB Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that stimulates BLySB Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that stimulates BLySB Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that stimulates BLySB Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0253] The present invention also provides for fusion proteins comprising, or alternatively consisting of, an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically binds to BLySB Lymphocyte Stimulator, and a heterologous polypeptide. Preferably, the heterologous polypeptide to which the antibody is fused to is useful for B-cell function or is useful to target the antibody to B-cells. In an alternative preferred embodiment, the heterologous polypeptide to which the antibody is fused to is useful for monocyte cell function or is useful to target the antibody to a monocyte. In another embodiment, the heterologous polypeptide to which the antibody is fused is albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-x of human serum albumin, where x is an integer from 1 to 585 and the albumin fragment has human serum albumin activity. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide).

[0254] In one embodiment, a fusion protein of the invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one or more of the VH domains referred to in Table 1 or the amino acid sequence of any one or more of the VL domains referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. In another embodiment, a fusion protein of the

present invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1, or the amino acid sequence of any one, two, three, or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. In a preferred embodiment, the fusion protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of, a VH CDR3 referred to in Table 1, or fragment or variant thereof, and a heterologous polypeptide sequence, which fusion protein immunospecifically binds to BLySB Lymphocyte Stimulator. In another embodiment, a fusion protein comprises, or alternatively consists of a polypeptide having the amino acid sequence of at least one VH domain referred to in Table 1 and the amino acid sequence of at least one VL domain referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, the VH and VL domains of the fusion protein correspond to the same scFv referred to in Table 1. In yet another embodiment, a fusion protein of the invention comprises, or alternatively consists of a polypeptide having the amino acid sequence of any one, two, three or more of the VH CDRs referred to in Table 1 and the amino acid sequence of any one, two, three or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, two, three, four, five, six, or more of the VHCDR(s) or VLCDR(s) correspond to the same scFv referred to in Table 1. Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention.

[0255] The present invention also provides: antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator; antibodies that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator; and antibodies that immunospecifically bind to both the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator.

[0256] In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1563 – 1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL

domains contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1, or fragment(s) or variant(s) (including derivative) thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained SEQ ID NOS: 1563 - 1880 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0257] In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino

acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0258] In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator, are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1 - 1562 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s

contained in SEQ ID NOS: 1 - 1562, disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1 - 1562, disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1.

[0259] The present invention also provides for mixtures of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator, wherein the mixture has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for mixtures of different antibodies that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the membrane-bound form and soluble form of BLySB Lymphocyte Stimulator. In specific embodiments, the invention provides mixtures of at least 2, preferably at least 4, at least 6, at least 8, at least 10, at least 12, at least 15, at least 20, or at least 25 different antibodies that immunospecifically bind to BLySB Lymphocyte Stimulator, wherein at least 1, at least 2, at least 4, at least 6, or at least 10, antibodies of the mixture is an antibody of the invention. In a specific embodiment, each antibody of the mixture is an antibody of the invention.

[0260] The present invention also provides for panels of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator, wherein the panel has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for panels of different antibodies that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator, the membrane-bound form of BLySB Lymphocyte Stimulator, and/or both the membrane-bound form and soluble form of BLySB Lymphocyte Stimulator. In specific embodiments, the invention provides for panels of antibodies that have different affinities for BLySB Lymphocyte Stimulator, different specificities for BLySB Lymphocyte Stimulator, or different dissociation rates. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least

850, at least 900, at least 950, or at least 1000, antibodies. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.

[0261] The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1563 - 1880, as disclosed in Table 1 or a variant thereof.

[0262] The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively

consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1 or a variant thereof.

[0263] The present invention further provides for compositions comprising, one or more antibodies (including scFvs, or molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1 or a variant thereof.

[0264] Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternative consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three,

four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s contained SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1, or a variant thereof.

[0265] Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1, or a variant thereof.

[0266] Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or

alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1 - 1562 as disclosed in Table 1, or a variant thereof.

[0267] In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains disclosed in Table 1, or a variant thereof, and an amino acid sequence of any one or more of the VL domains disclosed in Table 1, or a variant thereof wherein the VH and VL domains are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLySB Lymphocyte Stimulator (SEQ ID NOS:1563 - 1880), from scFvs that bind membrane-bound BLySB Lymphocyte Stimulator (SEQ ID 1881 - 2128), or from scFvs that bind both soluble and membrane-bound BLySB Lymphocyte Stimulator (SEQ ID NOS:1 - 1562). In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1,2, or 3) and VL CDRY (where Y= 1,2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble BLySB Lymphocyte Stimulator (SEQ ID NOS:1563 - 1880), from scFvs that bind membrane-bound BLySB Lymphocyte Stimulator (SEQ ID NOS:1881 - 2128), or from scFvs that bind both soluble and membrane-bound BLySB Lymphocyte Stimulator (SEQ ID NOS:1 - 1562). In yet

another embodiment, a composition of the present invention comprises one or more fusion proteins.

[0268] As discussed in more detail below, a composition of the invention may be used either alone or in combination with other compositions. The antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, *e.g.*, PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

[0269] Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may be used, for example, but not limited to, to purify and detect BLySB Lymphocyte Stimulator, and to target the polypeptides of the present invention to cells expressing membrane-bound BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of BLySB Lymphocyte Stimulator in biological samples. See, *e.g.*, Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

Methods Producing Antibodies

[0270] The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

[0271] The single chain Fvs disclosed in Table 1 were generated using phage display methods known in the art. Furthermore, other scFvs that immunospecifically bind BLySB Lymphocyte Stimulator may be generated using phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the

surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of lymphoid tissues) or synthetic cDNA libraries. The DNA encoding the VH and VL domains are joined together by an scFv linker by PCR and cloned into a phagemid vector (*e.g.*, p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to an antigen of interest (*i.e.*, BLySB Lymphocyte Stimulator or a fragment thereof) can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include, but are not limited to, those disclosed in Brinkman *et al.*, J. Immunol. Methods 182:41-50 (1995); Ames *et al.*, J. Immunol. Methods 184:177-186 (1995); Kettleborough *et al.*, Eur. J. Immunol. 24:952-958 (1994); Persic *et al.*, Gene 187 9-18 (1997); Burton *et al.*, Advances in Immunology 57:191-280(1994); PCT application No. PCT/GB91/O1 134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/1 1236; WO 95/15982; WO 95/20401; WO97/13844; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0272] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described below. Techniques to recombinantly produce Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax *et al.*, BioTechniques 12(6):864-869 (1992); Sawai *et al.*, AJRI 34:26-34 (1995); and Better *et al.*, Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0273] To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be

used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, *e.g.*, the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. Preferably, the vectors for expressing the VH or VL domains comprise a promoter suitable to direct expression of the heavy and light chains in the chosen expression system, a secretion signal, a cloning site for the immunoglobulin variable domain, immunoglobulin constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[0274] Cell lines that express antibodies that comprise the VH and VL domains of scFvs of the invention have been deposited with the American Type Culture Collection ("ATCCATCC™") on the dates listed in Table 2 and given the ATCCATCC™ Deposit Numbers identified in Table 2. The American Type Culture Collection ATCC is located at 10801 University Boulevard, Manassas, VA 20110-2209, USA. The ATCCATCC™ deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

Cell Line	Corresponding scFv	SEQ ID NO:	<u>ATCCATCC™</u> Deposit Number	<u>ATCCATCC™</u> Deposit Date
NSO-B11-15	I050B11-15	24	PTA-3238	March 27, 2001
NSO-anti-BLyS-6D08-18	I006D08	2	PTA-3239	March 27, 2001
NSO- anti-BLyS <u>B</u> <u>Lymphocyte Stimulator-</u> 116A01-60	I116A01	327	PTA-3240	March 27, 2001
IO26C04K	I026C04-K	1563	PTA-3241	March 27, 2001
IO50A12	I050A12	12	PTA-3242	March 27, 2001
IO50-B11	I050B11	9	PTA-3243	March 27, 2001

[0275] Accordingly, in one embodiment, the invention provides antibodies that comprise the VH and VL domains of scFvs of the invention.

[0276] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11-15.

[0277] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-anti-BLyS-6D08-18.

[0278] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO- anti-BLyS-116A01-60.

[0279] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line IO26C04K.

[0280] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line IO50A12.

[0281] In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11.

[0282] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a ~~B~~LySB Lymphocyte Stimulator polypeptide. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a ~~B~~LySB Lymphocyte Stimulator polypeptide by between 1% and 10% in a competitive inhibition assay. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a ~~B~~LySB Lymphocyte Stimulator polypeptide by between 1% and 10% in a competitive inhibition assay.

[0283] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a ~~B~~LySB Lymphocyte Stimulator polypeptide by at least 10% and up to 20% in a competitive inhibition assay.

[0284] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLySB Lymphocyte Stimulator polypeptide by at least 20% and up to 30% in a competitive inhibition assay.

[0285] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLySB Lymphocyte Stimulator polypeptide by at least 30% and up to 40% in a competitive inhibition assay.

[0286] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLySB Lymphocyte Stimulator polypeptide by at least 40% and up to 50% in a competitive inhibition assay.

[0287] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLySB Lymphocyte Stimulator polypeptide by at least 50% and up to 60% in a competitive inhibition assay.

[0288] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLySB Lymphocyte Stimulator polypeptide by at least 60% and up to 70% in a competitive inhibition assay.

[0289] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLySB Lymphocyte Stimulator polypeptide by at least 70% and up to 80% in a competitive inhibition assay.

[0290] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain,

VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLySB Lymphocyte Stimulator polypeptide by at least 80% and up to 90% in a competitive inhibition assay.

[0291] In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a BLySB Lymphocyte Stimulator polypeptide by at least 90% and up to 100% in a competitive inhibition assay.

[0292] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCATCC™ deposit number PTA-3238 to a BLySB Lymphocyte Stimulator polypeptide.

[0293] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCATCC™ deposit number PTA-3239 to a BLySB Lymphocyte Stimulator polypeptide.

[0294] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCATCC™ deposit number PTA-3240 to a BLySB Lymphocyte Stimulator polypeptide.

[0295] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCATCC™ deposit number PTA-3241 to a BLySB Lymphocyte Stimulator polypeptide.

[0296] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCATCC™ deposit number PTA-3242 to a BLySB Lymphocyte Stimulator polypeptide.

[0297] In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCATCC™ deposit number PTA-3243 to a BLySB Lymphocyte Stimulator polypeptide.

[0298] For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human patients. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety. In a specific embodiment, antibodies of the present invention comprise one or more VH and VL domains corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In a specific embodiment, antibodies of the present invention comprise one or more CDRs corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In other embodiments, an antibody of the present invention comprises one, two, three, four, five, six or more VL CDRs or VH CDRs corresponding to one or more of the human scFvs referred to in Table 1, or fragments or variants thereof, and framework regions (and, optionally CDRs not derived from the scFvs in Table 1) from a human immunoglobulin molecule. In a preferred embodiment, an antibody of the present invention comprises a VH CDR3, VL CDR3, or both, corresponding to the same scFv, or different scFvs referred to in Table 1, or fragments or variants thereof, and framework regions from a human immunoglobulin.

[0299] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a variable region derived from a human antibody and a non-human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See *e.g.*, Morrison, Science 229:1202 (1985); Oi *et al.*, BioTechniques 4:214 (1986); Gillies *et al.*, J. Immunol. Methods 125:191-202 (1989); U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Chimeric antibodies comprising one or more CDRs from human species and framework regions from a non-human immunoglobulin molecule (*e.g.*, framework regions from a canine or feline immunoglobulin molecule) can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or

resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka *et al.*, *Protein Engineering* 7(6):805-814 (1994); Roguska *et al.*, *PNAS* 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332). In a preferred embodiment, chimeric antibodies comprise a human CDR3 having an amino acid sequence of any one of the VH CDR3s or VL CDR3s referred to in Table 1, or a variant thereof, and non-human framework regions or human framework regions different from those of the frameworks in the corresponding scFv disclosed in Table 1. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, *e.g.*, Queen *et al.*, U.S. Patent No. 5,585,089; Riechmann *et al.*, *Nature* 332:323 (1988), which are incorporated herein by reference in their entireties.)

[0300] Further, the antibodies of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that “mimic” BLySB Lymphocyte Stimulator polypeptides using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, *FASEB J.* 7(5):437-444 (1993); and Nissinoff, *J. Immunol.* 147(8):2429-2438 (1991)). For example, antibodies of the invention which bind to BLySB Lymphocyte Stimulator and competitively inhibit the binding of BLySB Lymphocyte Stimulator to its receptor (as determined by assays well known in the art such as, for example, that disclosed, *infra*) can be used to generate anti-idiotypes that “mimic” a BLySB Lymphocyte Stimulator ligand/receptor-binding domain and, as a consequence, bind to and neutralize BLySB Lymphocyte Stimulator receptors (*e.g.*, TACI, BCMA, and TR20). Such neutralizing anti-idiotypes (including molecules comprising, or alternatively consisting of, antibody fragments or variants, such as Fab fragments of such anti-idiotypes) can be used in therapeutic regimens to neutralize BLySB Lymphocyte Stimulator. For example, such anti-idiotypic antibodies can be used to bind BLySB Lymphocyte Stimulator ligands/receptors, and thereby block BLySB Lymphocyte Stimulator mediated biological activity. Alternatively, anti-idiotypes that “mimic” a BLySB Lymphocyte Stimulator binding domain may bind to BLySB Lymphocyte Stimulator receptor(s) and induce

BLySB Lymphocyte Stimulator receptor mediated signalling (e.g., activation of nuclear factor of activated T cells (NF-AT), nuclear factor-kappa B (NF-kappa B), and/or AP-1). Such agonistic anti-idiotypes (including agonistic Fab fragments of these anti-idiotypes) can be used in therapeutic regimens to induce or enhance BLySB Lymphocyte Stimulator receptor mediated signalling. For example, such anti-idiotypic antibodies can be used to bind BLySB Lymphocyte Stimulator ligands/receptors, and thereby stimulate BLySB Lymphocyte Stimulator mediated biological activity (e.g., B cell proliferation and/or immunoglobulin production).

[0301] Once an antibody molecule of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) has been chemically synthesized or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, a protein molecule, such as, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

Polynucleotides Encoding an Antibody

[0302] The invention provides polynucleotides comprising, or alternatively consisting of, a nucleotide sequence encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). The invention also encompasses polynucleotides that hybridize under high stringency, or alternatively, under intermediate or lower stringency hybridization conditions, *e.g.*, as defined *supra*, to polynucleotides complementary to nucleic acids having a polynucleotide sequence that encodes an antibody of the invention or a fragment or variant thereof.

[0303] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Since the amino acid sequences of the scFv antibodies and VH domains, VL domains and CDRs thereof, are known (as described in Table 1), nucleotide sequences encoding these antibodies can be

determined using methods well known in the art, *i.e.*, the nucleotide codons known to encode the particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody, of the invention. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier *et al.*, BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0304] Alternatively, a polynucleotide encoding an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (*e.g.*, an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A⁺ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0305] Once the nucleotide sequence of the antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, *e.g.*, recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook *et al.*, 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel *et al.*, eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0306] In a specific embodiment, one or more of the VH and VL domains referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. In a specific embodiment, one, two, three, four, five, six, or more of the CDRs referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, *e.g.*, Chothia *et al.*, J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions, the contents of which are hereby incorporated by reference in its entirety). Preferably, the polynucleotides generated by the combination of the framework regions and CDRs encode an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically binds to ~~BLySB~~ Lymphocyte Stimulator. Preferably, as discussed *supra*, polynucleotides encoding variants of antibodies or antibody fragments having one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules, or antibody fragments or variants, lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and fall within the ordinary skill of the art.

Recombinant Expression of an Antibody

[0307] Recombinant expression of an antibody of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (*e.g.*, a heavy or light chain of an antibody of the invention or a portion thereof or a single chain antibody of the invention)), requires construction of an expression vector(s) containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule (*e.g.*, a whole antibody, a heavy or light chain of an antibody, or portion thereof (preferably, but not necessarily, containing the heavy or light chain variable domain)), of the invention has been obtained, the vector(s) for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by

expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention (e.g., a whole antibody, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody, or a portion thereof, or a heavy or light chain CDR, a single chain Fv, or fragments or variants thereof), operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464, the contents of each of which are hereby incorporated by reference in its entirety) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy chain, the entire light chain, or both the entire heavy and light chains.

[0308] The expression vector(s) is(are) transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing polynucleotide(s) encoding an antibody of the invention (e.g., whole antibody, a heavy or light chain thereof, or portion thereof, or a single chain antibody of the invention, or a fragment or variant thereof), operably linked to a heterologous promoter. In preferred embodiments, for the expression of entire antibody molecules, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0309] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include, but are not limited to, microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces*,

Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking *et al.*, Gene 45:101 (1986); Cockett *et al.*, Bio/Technology 8:2 (1990)).

[0310] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther *et al.*, EMBO 1. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0311] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. Antibody coding sequences may be cloned individually into non-essential regions (for example, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example, the polyhedrin promoter).

[0312] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region EI or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (*e.g.*, see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, *e.g.*, Bittner *et al.*, Methods in Enzymol. 153:51-544 (1987)).

[0313] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, NSO, MDCK, 293, 3T3, W138, and in particular, breast

cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and HsS78Bst.

[0314] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

[0315] A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler *et al.*, Cell 11:223 (1977)), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy *et al.*, Cell 22:8 17 (1980)) genes can be employed in tk-, hgp^{rt}- or ap^{rt}- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler *et al.*, Natl. Acad. Sci. USA 77:357 (1980); O'Hare *et al.*, Proc. Natl. Acad. Sci. USA 78:1527 (1981)); *gpt*, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 (Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62: 191-217 (1993); TIB TECH 11(5):155-2 15 (May, 1993)); and *hygro*, which confers resistance to hygromycin (Santerre *et al.*, Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described,

for example, in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli *et al.* (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin *et al.*, J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[0316] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the coding sequence of the antibody, production of the antibody will also increase (Crouse *et al.*, Mol. Cell. Biol. 3:257 (1983)).

[0317] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain is preferably placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2 197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0318] Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, for purification of a protein, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

Antibody Characterization

[0319] Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be characterized in a variety of ways. In particular, antibodies and related molecules of the invention may be assayed for the ability to immunospecifically bind to BLySB Lymphocyte Stimulator or a fragment of BLySB Lymphocyte Stimulator (e.g., to the soluble form or the membrane-bound form of BLySB Lymphocyte Stimulator) using techniques described herein or routinely modifying techniques known in the art. BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator fragments that may be immunospecifically bound by the compositions of the invention include, but are not limited to, human BLySB Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or BLySB Lymphocyte Stimulator expressed on human monocytes; murine BLySB Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or BLySB Lymphocyte Stimulator expressed on murine monocytes; rat BLySB Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey BLySB Lymphocyte Stimulator (e.g., the monkey BLySB Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLySB Lymphocyte Stimulator, or BLySB Lymphocyte Stimulator expressed on monkey monocytes) or fragments thereof. Preferably compositions of the invention bind human BLySB Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or fragments thereof. Assays for the ability of the antibodies of the invention to immunospecifically bind BLySB Lymphocyte Stimulator or a fragment of BLySB Lymphocyte Stimulator may be performed in solution (e.g., Houghten, Bio/Techniques 13:412-421(1992)), on beads (e.g., Lam, Nature 354:82-84 (1991)), on chips (e.g., Fodor, Nature 364:555-556 (1993)), on bacteria (e.g., U.S. Patent No. 5,223,409), on spores (e.g., Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (e.g., Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (e.g., Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404-406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Antibodies that have been identified to immunospecifically bind to BLySB Lymphocyte Stimulator or a fragment of BLySB Lymphocyte Stimulator can then be

assayed for their specificity and affinity for BLySB Lymphocyte Stimulator or a fragment of BLySB Lymphocyte Stimulator using or routinely modifying techniques described herein or otherwise known in the art.

[0320] The antibodies of the invention may be assayed for immunospecific binding to BLySB Lymphocyte Stimulator and cross-reactivity with other antigens by any method known in the art. In particular, the ability of an antibody to immunospecifically bind to the soluble form or membrane-bound form of BLySB Lymphocyte Stimulator and the specificity of the antibody, fragment, or variant for BLySB Lymphocyte Stimulator polypeptide from a particular species (e.g., murine, monkey or human, preferably human) may be determined using or routinely modifying techniques described herein or otherwise known in art .

[0321] Immunoassays which can be used to analyze immunospecific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), “sandwich” immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0322] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40 degrees C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as

to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[0323] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

[0324] ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound antibodies or non-specifically bound antibodies, and detecting the presence of the antibodies specifically bound to the antigen coating the well. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as

an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[0325] The binding affinity of an antibody (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, ^3H or ^{125}I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of the present invention for BLySB Lymphocyte Stimulator and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, BLySB Lymphocyte Stimulator is incubated with an antibody of the present invention conjugated to a labeled compound (*e.g.*, ^3H or ^{125}I) in the presence of increasing amounts of an unlabeled second anti-BLySB Lymphocyte Stimulator antibody.

[0326] In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibodies (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to BLySB Lymphocyte Stimulator, or fragments of BLySB Lymphocyte Stimulator. BIAcore kinetic analysis comprises analyzing the binding and dissociation of BLySB Lymphocyte Stimulator from chips with immobilized antibodies on their surface as described in detail in Examples 6, 12, 17 and 18, *infra*.

[0327] The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can also be assayed for their ability to inhibit, increase, or not significantly alter, the binding of BLySB Lymphocyte Stimulator to a BLySB Lymphocyte Stimulator receptor (*e.g.*, TACI and BCMA) using techniques known to those of skill in the art. For example, cells expressing a receptor for BLySB Lymphocyte Stimulator (*e.g.*, IM9, REH, ARH-77cells, Namalwa, and RPMI-8226 B cell tumor lines as well as peripheral CD20+ B cells) can be

contacted with BLySB Lymphocyte Stimulator in the presence or absence of an antibody, and the ability of the antibody to inhibit, increase, or not significantly alter, BLySB Lymphocyte Stimulator binding to the cells can be measured. BLySB Lymphocyte Stimulator binding to cells can be measured by, for example, flow cytometry or a scintillation assay. BLySB Lymphocyte Stimulator or the antibody can be labeled with a detectable compound such as a radioactive label (*e.g.*, ^{32}P , ^{35}S , and ^{125}I) or a fluorescent label (*e.g.*, fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine) to enable detection of an interaction between BLySB Lymphocyte Stimulator and a BLySB Lymphocyte Stimulator receptor and/or BLySB Lymphocyte Stimulator and an antibody of the invention. Alternatively, the ability of antibodies of the invention to inhibit, increase, or not significantly alter, BLySB Lymphocyte Stimulator binding to a BLySB Lymphocyte Stimulator receptor can be determined in cell-free assays. For example, native or recombinant BLySB Lymphocyte Stimulator (*e.g.*, that having the amino acid sequence of amino acids 134 – 285 of SEQ ID NO:3228) or a fragment thereof can be contacted with an antibody and the ability of the antibody to inhibit, increase, or not significantly alter, BLySB Lymphocyte Stimulator from binding to a BLySB Lymphocyte Stimulator receptor can be determined. Preferably, the antibody is immobilized on a solid support and BLySB Lymphocyte Stimulator or a BLySB Lymphocyte Stimulator fragment is labeled with a detectable compound. Alternatively, BLySB Lymphocyte Stimulator or a BLySB Lymphocyte Stimulator fragment is immobilized on a solid support and the antibody is labeled with a detectable compound. BLySB Lymphocyte Stimulator may be partially or completely purified (*e.g.*, partially or completely free of other polypeptides) or part of a cell lysate. Further, the BLySB Lymphocyte Stimulator polypeptide may be a fusion protein comprising BLySB Lymphocyte Stimulator or a biologically active portion thereof and a domain such as an Immunoglobulin Fc or glutathionine-S-transferase. For example, amino acid residues 1-154 of TACI (GenBank accession number AAC51790), or 1-48 of BCMA (GenBank accession number NP_001183) may be fused to the Fc region of an IgG molecule and used in a cell free assay to determine the ability of antibodies of the invention to inhibit, increase, or not significantly alter, BLySB Lymphocyte Stimulator binding to a BLySB Lymphocyte Stimulator receptor. Alternatively, BLySB Lymphocyte

Stimulator can be biotinylated using techniques well known to those of skill in the art (e.g., biotinylation kit, Pierce Chemicals; Rockford, IL).

[0328] The antibodies of the invention (including scFvs or other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can also be assayed for their ability to inhibit, stimulate, or not significantly alter, BLySB Lymphocyte Stimulator-induced B-cell proliferation using techniques known to those of skill in the art. For example, B-cell proliferation can be assayed by ³H-thymidine incorporation assays and trypan blue cell counts (see, e.g., Moore *et al.*, Science 285: 260-263 (1999)). Further, the antibodies of the invention, or fragments or variants thereof, can be assayed for their ability to block, stimulate, or not significantly alter, BLySB Lymphocyte Stimulator-induced activation of cellular signaling molecules and transcription factors such as calcium-modulator and cyclophilin ligand ("CAML"), calcineurin, nuclear factor of activated T cells transcription factor ("NF-AT"), nuclear factor-kappa B ("NF-kappa B"), and AP-1 using techniques known to those of skill in the art (see, e.g., von Bulow and Bram, Science 278:138-141(1997)). For example, NF-AT activity can be determined by electromobility gel shift assays, by detecting the expression of a protein known to be regulated by NF-AT (e.g., IL-2 expression), by detecting the induction of a reporter gene (e.g., an NF-AT regulatory element operably linked to a nucleic acid encoding a detectable marker such as luciferase, beta-galactosidase or chloramphenicol acetyltransferase (CAT)), or by detecting a cellular response (e.g., cellular differentiation, or cell proliferation).

[0329] The antibodies of the invention, or fragments or variants thereof can also be assayed for their ability to neutralize, enhance, or not significantly alter, BLySB Lymphocyte Stimulator activity. For example, antibodies or fragments or variants thereof, may be routinely tested for their ability to inhibit BLySB Lymphocyte Stimulator from binding to cells expressing the receptor for BLySB Lymphocyte Stimulator (see Example 3, *infra*).

Selection and Screening for Antibodies that Immunospecifically Bind to Soluble BLySB Lymphocyte Stimulator

[0330] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be

screened in a variety of assays to identify those antibodies that immunospecifically bind to the soluble form of BLySB Lymphocyte Stimulator. In one particular assay, antibodies that bind to the biotinylated soluble form of BLySB Lymphocyte Stimulator in solution are captured on streptavidin coated magnetic beads. This assay may be relatively applied to identify antibodies of the invention that neutralize and/or bind to BLySB Lymphocyte Stimulator. Additionally, antibodies may be assayed in neutralization assays described herein or otherwise known in the art (see Example 3, *infra*). For example, antibodies may be tested for their ability to inhibit soluble BLySB Lymphocyte Stimulator (e.g., biotinylated BLySB Lymphocyte Stimulator) from binding to IM9 cells. In this assay, labeled soluble BLySB Lymphocyte Stimulator (e.g., biotinylated BLySB Lymphocyte Stimulator) is incubated with candidate anti-BLySB Lymphocyte Stimulator antibodies to allow for the formation of BLySB Lymphocyte Stimulator -anti-BLySB Lymphocyte Stimulator antibody complexes. Following incubation, an aliquot of the BLySB Lymphocyte Stimulator-anti-BLySB Lymphocyte Stimulator antibody sample is added to IM9 cells. The binding of soluble BLySB Lymphocyte Stimulator may be determined using techniques known in the art. For example, the binding of biotinylated BLySB Lymphocyte Stimulator to IM9 cells may be detected using a fluorimeter following the addition of streptavidin-delfia. Biotinylated BLySB Lymphocyte Stimulator, if it is not bound by antibodies that neutralize BLySB Lymphocyte Stimulator, binds to the cells is detected. Thus, an antibody that decreases the amount of bio-BLySB Lymphocyte Stimulator that binds to IM-9 cells (relative to a control sample in which the BLySB Lymphocyte Stimulator had been preincubated with an irrelevant antibody or no antibody at all) is identified as one that binds to and neutralizes the soluble form of BLySB Lymphocyte Stimulator. In another assay, antibodies are screened using ELISAs for those antibodies that bind to biotinylated soluble BLySB Lymphocyte Stimulator, but do not bind membrane-bound BLySB Lymphocyte Stimulator, such as, for example, BLySB Lymphocyte Stimulator on membranes from U937 cells (see Examples 2 and 9, *infra*). In these assays, soluble BLySB Lymphocyte Stimulator (e.g., biotinylated BLySB Lymphocyte Stimulator) and membrane-bound BLySB Lymphocyte Stimulator (e.g., on U937 membranes) are incubated in separate samples with the same antibodies and those antibodies that bind to the soluble BLySB Lymphocyte Stimulator (biotinylated BLySB

Lymphocyte Stimulator), but not membrane-bound BLySB Lymphocyte Stimulator (e.g., on U937 membranes) are captured and identified.

[0331] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be tested to identify those antibodies that do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (see Example 4, *infra*). Antibodies may also be tested for their affinity for BLySB Lymphocyte Stimulator using, for example, BIAcore analysis (see Examples 6, 12, 17 and 18 *infra*). Antibodies may also be tested for their ability to stimulate, inhibit, or not alter, BLySB Lymphocyte Stimulator-induced immunoglobulin production and/or B-cell proliferation using techniques known to those of skill in the art. For example, human B-cells, BLySB Lymphocyte Stimulator and antibodies may be incubated together in 96 well plates and ³H-thymidine incorporation may be measured using a scintillation counter.

Selection and Screening for Antibodies that Immunospecifically Bind to Membrane-bound BLySB Lymphocyte Stimulator

[0332] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator. In one particular assay, antibodies that bind to BLySB Lymphocyte Stimulator on U937 membranes or immobilized histidine-tagged BLySB Lymphocyte Stimulator are captured. Other cell lines that express BLySB Lymphocyte Stimulator that might be useful for testing antibody binding to membrane-bound form of BLySB Lymphocyte Stimulator include, K-562, HL-60 and THP-1 cells. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that bind to BLySB Lymphocyte Stimulator on U937 membranes or to histidine-tagged BLySB Lymphocyte Stimulator. In this assay, antibodies are added to 96 well plates coated with U937 membranes or histidine-tagged BLySB Lymphocyte Stimulator and those antibodies or antibody fragments or variants that bind to the U937 membranes or histidine-tagged BLySB Lymphocyte Stimulator are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants thereof) that do not bind to biotinylated BLySB

Lymphocyte Stimulator (soluble BLySB Lymphocyte Stimulator) but bind to membrane-bound BLySB Lymphocyte Stimulator, such as, for example, that on membranes from U937 cells (see Example 2, *infra*). In these assays, soluble BLySB Lymphocyte Stimulator (e.g., biotinylated BLySB Lymphocyte Stimulator) and membrane-bound BLySB Lymphocyte Stimulator (e.g., on U937 membranes) are incubated in separate samples with the same antibodies (or antibody fragments or variants) and those antibodies (or antibody fragments or variants) that do not bind to the soluble BLySB Lymphocyte Stimulator (biotinylated BLySB Lymphocyte Stimulator), but bind the membrane-bound BLySB Lymphocyte Stimulator (e.g., on U937 membranes) are captured and identified. In other assays, antibodies are screened using ELISAs to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged BLySB Lymphocyte Stimulator or membranes from U937 cells do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (See Example 4, *infra*). ELISAs can also be used to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged BLySB Lymphocyte Stimulator or membranes from U937 cells bind to BLySB Lymphocyte Stimulator in the presence of TNF-alpha (see Example 4, *infra*). Antibodies or fragments or variants thereof that immunospecifically bind to the membrane-bound form of BLySB Lymphocyte Stimulator may also be tested for their affinity for histidine-tagged BLySB Lymphocyte Stimulator using high-throughput BIAcore analysis (see Example 14, *infra*).

[0333] Additionally, antibodies of the invention may be screened against cells engineered to express an “uncleavable” form of BLySB Lymphocyte Stimulator in order to determine their specificity for the membrane-bound form of BLySB Lymphocyte Stimulator. Mutations in BLySB Lymphocyte Stimulator which may achieve this result include, but are not limited to, the mutation or deletion of amino acid residues Lys-132 and/or Arg-133 of the BLySB Lymphocyte Stimulator sequence shown in SEQ ID NO:3228. A typical mutagenesis might include mutation of one or both of residues Lys-132 or Arg-133 to alanine residues. Cells expressing such an “uncleavable” form of BLySB Lymphocyte Stimulator provide a profound reagent to use in assaying the ability of antibodies to bind the membrane-bound form of BLySB Lymphocyte Stimulator.

Selection and Screening for Antibodies that Immunospecifically Bind to Soluble and Membrane-bound BLySB Lymphocyte Stimulator

[0334] Antibodies of the invention (including scFvs and other molecules comprising, or alternately consisting of, antibody fragments or variants) may be screened in a variety of assays to identify those antibodies or antibody fragments or variants that immunospecifically bind to the soluble form and membrane-bound form of BLySB Lymphocyte Stimulator. In one particular assay, antibodies that bind to immobilized BLySB Lymphocyte Stimulator are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that inhibit the binding of soluble BLySB Lymphocyte Stimulator (e.g. soluble bio-BLySB Lymphocyte Stimulator) to IM-9 cells as described *supra*. In other assays, antibodies are screened using ELISAs for those antibodies that bind to membranes from U937 cells. Additionally, further ELISA assays may be performed using techniques known in the art to determine which antibodies do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS, or those antibodies that bind to BLySB Lymphocyte Stimulator in the presence of TNF-alpha (see Example 4 *infra*). Antibodies may be assayed in neutralization assays using techniques described herein or otherwise known in the art. Antibodies that immunospecifically bind to the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator may also be tested for their affinity for BLySB Lymphocyte Stimulator using high-throughput BIAcore analysis.

Antibody Conjugates

[0335] The present invention encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous polypeptide (or portion thereof, preferably at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids of the polypeptide) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies of the invention may be used to target heterologous polypeptides to particular cell types (e.g., cells of monocytic lineage and B-cells), either *in vitro* or *in vivo*, by fusing or conjugating the heterologous polypeptides to antibodies of the invention that

are specific for particular cell surface antigens (e.g., membrane-bound BLySB Lymphocyte Stimulator on cells of monocytic lineage) or which bind antigens that bind particular cell surface receptors (e.g., TACI and/or BCMA located on B cells). Antibodies fused or conjugated to heterologous polypeptides may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See *e.g.*, Harbor *et al.*, *supra*, and PCT publication WO 93/2 1232; EP 439,095; Naramura *et al.*, *Immunol. Lett.* 39:91-99 (1994); U.S. Patent 5,474,981; Gillies *et al.*, *PNAS* 89:1428-1432 (1992); Fell *et al.*, *J. Immunol.* 146:2446-2452 (1991), which are incorporated by reference in their entireties.

[0336] In one embodiment, a fusion protein comprises a polypeptide having an amino acid sequence of any one of the VH domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 (i.e., SEQ ID NOS:2129 - 3227), and a heterologous polypeptide.

[0337] In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, and a heterologous polypeptide. In yet another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR3s referred to in Table 1, and a heterologous polypeptide.

[0338] In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, and one or more VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein of the present invention comprises a polypeptide having the

amino acid sequence of any one of the VH CDRs referred to in Table 1, and any one of the VL CDRs referred to in Table 1, and a heterologous polypeptide.

[0339] The present invention further includes compositions comprising, or alternatively consisting of, heterologous polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)₂ fragment, or a portion thereof. Methods for fusing or conjugating polypeptides to antibody portions are known in the art. See, *e.g.*, U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 9 1/06570; Ashkenazi *et al.*, Proc. Natl. Acad. Sci. USA 88: 10535-10539 (1991); Zheng *et al.*, J. Immunol. 154:5590-5600 (1995); and Vil *et al.*, Proc. Natl. Acad. Sci. USA 89:11337- 11341 (1992) (said references incorporated by reference in their entireties).

[0340] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), such methods can be used to generate antibodies with altered activity (*e.g.*, antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten *et al.*, Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, *et al.*, J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, polynucleotides encoding antibodies of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more portions of a polynucleotide encoding an antibody which portions immunospecifically bind to BLySB Lymphocyte Stimulator may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0341] Moreover, the antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants

thereof), can be fused to marker sequences, such as a polypeptides to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexahistidine polypeptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexahistidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, Cell 37:767 (1984)) and the "flag" tag (DYKDDDDK, (SEQ ID No: 3238) Stratagene, La Jolla, CA).

[0342] The present invention further encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor or prognose the development or progression of a tumor as part of a clinical testing procedure to, *e.g.*, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include, but are not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include, but are not limited to, streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include, but are not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes, but is not limited to, luminol; examples of bioluminescent materials include, but are not limited to, luciferase, luciferin, and aequorin; and examples of suitable radioactive

material include, but are not limited to, iodine (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru , ^{68}Ge , ^{57}Co , ^{65}Zn , ^{85}Sr , ^{32}P , ^{153}Gd , ^{169}Yb , ^{51}Cr , ^{54}Mn , ^{75}Se , ^{113}Sn , and ^{117}Tm .

[0343] Further, an antibody of the invention (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof), may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi . In specific embodiments, antibodies of the invention are attached to macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{111}In , ^{177}Lu , ^{90}Y , ^{166}Ho , and ^{153}Sm , to polypeptides. In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is ^{111}In . In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is ^{90}Y . In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, the DOTA is attached to the antibody of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90, 1998; Peterson et al., Bioconjug. Chem. 10(4):553-7, 1999; and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety.

[0344] A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells and includes such molecules as small molecule toxins and enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof. Examples include, but are not limited to, paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide (VP-16), teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, thymidine kinase, endonuclease, RNase, and puromycin and fragments, variants or homologs thereof. Therapeutic agents include, but are not limited to,

antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine), improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramidate, triethylenethiophosphoramidate trimethylolomelamine, chlornaphazine, cholophosphamide, estramustine, ifosfamide, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine, aclacinomysins, azaserine, cactinomycin, calichearnicin, carabycin, carminomycin, carzinophilin, chromomycins, detorubicin, 6-diazo-5-oxo-L-norleucine, epirubicin, esorubicin, idarubicin, marcellomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, quelamycin, rodorubicin, streptonigrin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, thiamiprine, ancitabine, azacitidine, 6-azauridine, carmofur, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU, calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, dernecolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, mitoguazone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, PSKO, razoxane, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2, 2',2''-trichlorotriethylamine, urethan, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), taxoids, *e.g.* paclitaxel (TAXOL", Bristol-Myers Squibb Oncology, Princeton, NJ) doxetaxel (TAXOTERE", Rh6ne-Poulenc Rorer, Antony, France), gemcitabine, ifosfamide, vinorelbine, navelbine, novantrone, teniposide, aminopterin, xeloda, ibandronate, CPT-I 1, topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), retinoic acid, esperamicins, capecitabine, and pharmaceutically acceptable salts, acids or derivatives of any of the

above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4 hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, toremifene (Fareston), and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin, and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0345] Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety) and direct coupling reactions (e.g., Bolton-Hunter and Chloramine-T reaction).

[0346] The antibodies of the invention which are conjugates can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, but are not limited to, for example, a toxin such as abrin, ricin A, alpha toxin, pseudomonas exotoxin, or diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), or other growth factors.

[0347] Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), may also be attached to solid supports, which are particularly useful for immunoassays or

purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0348] Techniques for conjugating a therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, “Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy”, in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, “Antibodies For Drug Delivery”, in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, “Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review”, in *Monoclonal Antibodies ‘84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); “Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy”, in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, “The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates”, *Immunol. Rev.* 62:119-58 (1982).

[0349] Alternatively, an antibody of the invention can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0350] An antibody of the invention (including an scFv or and other molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Use of Antibodies for Epitope Mapping

[0351] The present invention provides antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that can be used to identify epitopes of BLySB Lymphocyte Stimulator. In particular, the antibodies of the present invention can be used to identify epitopes of human BLySB Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or BLySB Lymphocyte Stimulator expressed on human monocytes; murine BLySB Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or BLySB Lymphocyte Stimulator expressed on murine monocytes; rat BLySB Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form,

e.g., on the surface of rat monocytes); or monkey BLySB Lymphocyte Stimulator (*e.g.*, the monkey BLySB Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLySB Lymphocyte Stimulator, or BLySB Lymphocyte Stimulator expressed on monkey monocytes) using techniques described herein or otherwise known in the art. Fragments which function as epitopes may be produced by any conventional means. (See, *e.g.*, Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211.)

Diagnostic Uses of Antibodies

[0352] Labeled antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor diseases and/or disorders associated with the aberrant expression and/or activity of BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of aberrant expression.

[0353] By “biological sample” is intended any fluids and/or cells obtained from an individual, body fluid, body tissue, body cell, cell line, tissue culture, or other source which may contain BLySB Lymphocyte Stimulator protein or mRNA. Body fluids include, but are not limited to, sera, plasma, urine, synovial fluid, spinal fluid, saliva, and mucous. Tissues samples may be taken from virtually any tissue in the body. Tissue samples may also be obtained from autopsy material. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0354] The invention also provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator receptor comprising (a) assaying the expression of

BLySB Lymphocyte Stimulator receptor in a biological sample from an individual using one or more antibodies or fragments or variants thereof that immunospecifically binds only to soluble BLySB Lymphocyte Stimulator, but does not inhibit BLySB Lymphocyte Stimulator /BLySB Lymphocyte Stimulator receptor binding. Such an antibody, by way of an example that is not to be construed as limiting, would be one that is able to capture a biotinylated BLySB Lymphocyte Stimulator from solution (see Example 8), but that would not prevent BLySB Lymphocyte Stimulator from binding to IM-9 cells (see Example 3). and (b) comparing the level of BLySB Lymphocyte Stimulator receptor with a standard level of BLySB Lymphocyte Stimulator receptor, *e.g.*, in normal tissue or cell samples, whereby an increase or decrease in the assayed level of BLySB Lymphocyte Stimulator receptor compared to the standard level of BLySB Lymphocyte Stimulator receptor is indicative of aberrant expression.

[0355] Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of BLySB Lymphocyte Stimulator is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of BLySB Lymphocyte Stimulator is indicative of an immunodeficiency.

[0356] Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to BLySB Lymphocyte Stimulator but, do not inhibit BLySB Lymphocyte Stimulator/ BLySB Lymphocyte Stimulator receptor binding can be used for diagnostic

purposes to detect, diagnose, prognose, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator receptor comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator receptor in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator receptor with a standard level of BLySB Lymphocyte Stimulator receptor, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of BLySB Lymphocyte Stimulator receptor compared to the standard level of BLySB Lymphocyte Stimulator receptor is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of BLySB Lymphocyte Stimulator receptor is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of BLySB Lymphocyte Stimulator receptor is indicative of an immunodeficiency.

[0357] Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (*e.g.*, IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (*e.g.*, Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, diabetes mellitus (*e.g.* Type I diabetes mellitus or insulin dependent diabetes mellitus), juvenile onset diabetes, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (*i.e.*, Hashimoto's thyroiditis, systemic lupus erythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease,

polymyositis/dermatomyositis, pernicious anemia (Addison's disease), idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomyopathy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders and other disorders such as inflammatory skin diseases including psoriasis and sclerosis, responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), respiratory distress syndrome (including adult respiratory distress syndrome, ARDS), meningitis, encephalitis, colitis, allergic conditions such as eczema and other conditions involving infiltration of T cells and chronic inflammatory responses, atherosclerosis, leukocyte adhesion deficiency, Reynaud's syndrome, and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, granulomatosis and diseases involving leukocyte diapedesis, central nervous system (CNS) inflammatory disorder, multiple organ injury syndrome, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, Lambert-Eaton myasthenic syndrome, Behcet disease, giant cell arteritis, immune complex nephritis, IgA nephropathy, IgM polyneuropathies or autoimmune thrombocytopenia etc.

[0358] In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

[0359] Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia,

dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

[0360] Elevated levels of soluble BLySB Lymphocyte Stimulator have been observed in the serum of patients with Systemic Lupus Erythematosus (SLE). In comparing the sera of 150 SLE patients with that of 38 control individuals, it was found that most of the SLE patients had more than 5ng/ml of serum BLySB Lymphocyte Stimulator, more than 30% of SLE patients had levels greater than 10ng/ml, and approximately 10% of SLE patients had serum BLySB Lymphocyte Stimulator levels greater than 20ng/ml. In contrast, the majority of normal controls had BLySB Lymphocyte Stimulator levels less than 5ng/ml, and less than 10% had levels higher than 10ng/ml. The elevated levels of BLySB Lymphocyte Stimulator protein in sera is present in the soluble form and has biologic activity as assayed by the ability to stimulate anti-IgM treated B cells in vitro. SLE patients with more than 15ng/ml serum BLySB Lymphocyte Stimulator were also found to have elevated levels of anti-dsDNA antibodies compared to both normal controls and SLE patients with less than 5ng/ml of serum BLySB Lymphocyte Stimulator. (unpublished data).

[0361] In addition the serum of two subgroups of patients which were positive for anti-nuclear antibodies (ANA+) but did not meet the formal requirements of the American College of Rheumatology (ACR) for classification of SLE were analyzed for BLySB Lymphocyte Stimulator levels. The first subgroup of sera was ANA+ sera that came from

patients who did not present with the clinical impression of SLE. This group had only slightly elevated levels of BLySB Lymphocyte Stimulator (~9ng/ml BLySB Lymphocyte Stimulator). The second subgroup however, which was ANA+ sera from patients who presented with the clinical impression of SLE, had significantly increased BLySB Lymphocyte Stimulator levels (~15ng/ml). These results suggest that an elevated level of BLySB Lymphocyte Stimulator precedes the formal fulfillment of the ACR criteria. The ACR criteria are described in Tan, E.M., et al, *Arthritis and Rheumatism* 25:1271 – 1277 (1982).

[0362] Thus in specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Systemic Lupus Erythematosus or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of SLE.

[0363] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor IgA nephropathy or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of IgA nephropathy.

[0364] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to

detect, diagnose, prognose, or monitor Sjögren's Syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of Sjögren's Syndrome.

[0365] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor HIV infection or conditions associated therewith (e.g. AIDS). The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of HIV infection.

[0366] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Myasthenia Gravis or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of Myasthenia Gravis.

[0367] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor idiopathic thrombocytopenic purpura (ITP) or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of idiopathic thrombocytopenic purpura (ITP).

[0368] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor hemolytic anemia or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of hemolytic anemia.

[0369] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor thyroiditis or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, *e.g.*, in normal biological samples, whereby an increase in the assayed level of

BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of thyroiditis.

[0370] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Goodpasture's syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of Goodpasture's syndrome.

[0371] In other specific embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor multiple sclerosis or conditions associated therewith. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, *e.g.*, in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of multiple sclerosis.

[0372] In additional embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Rheumatoid Arthritis. The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample (*e.g.*, serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte

Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of Rheumatoid arthritis.

[0373] In additional embodiments, antibodies of the invention which specifically bind to BLySB Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor an immune-based rheumatologic disease, (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), Polymyositis/dermatomyositis, Microscopic polyangiitis, Hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder). The invention provides for the detection of aberrant expression of BLySB Lymphocyte Stimulator comprising: (a) assaying the expression of BLySB Lymphocyte Stimulator in a biological sample (e.g., serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard level of BLySB Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of BLySB Lymphocyte Stimulator compared to the standard level of BLySB Lymphocyte Stimulator is indicative of monitor an immune-based rheumatologic disease.

[0374] It has been observed, that serum BLySB Lymphocyte Stimulator levels inversely correlate with nephrotic range proteinuria (>3gm proteinuria in a 24 hour urine collection) using a sample of 71 SLE patients (p=0.019). Proteinuria was determined in 71 SLE patients within one month of phlebotomy for serum BLySB Lymphocyte Stimulator determination. Serum BLySB Lymphocyte Stimulator was classified as low, normal, or high based on the 5th through 95th percentiles for normal controls. Nephrotic-range proteinuria was inversely correlated with serum Neutrokin- α levels. Thus, in specific embodiments, serum levels of BLySB Lymphocyte Stimulator (determined using one or more antibodies of the present invention) in individuals diagnosed with an immune based rheumatologic disease (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), seronegative spondyloarthropathy (SpA), polymyositis/dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis,

Takayasu's arteritis, and undifferentiated connective tissue disorder) may be used to determine, diagnose, prognose, or monitor the severity of certain aspects or symptoms of the disease, such as nephrotic-range proteinuria.

[0375] In another specific embodiment, antibodies of the invention are used to diagnose, prognose, treat, or prevent conditions associated with CVID, including, but not limited to, conditions associated with acute and recurring infections (e.g., pneumonia, bronchitis, sinusitis, otitis media, sepsis, meningitis, septic arthritis, and osteomyelitis), chronic lung disease, autoimmunity, granulomatous disease, lymphoma, cancers (e.g., cancers of the breast, stomach, colon, mouth, prostate, lung, vagina, ovary, skin, and melanin forming cells (i.e. melanoma), inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, and ulcerative proctitis), malabsorption, Hodgkin's disease, and Waldenstrom's macroglobulinemia.

[0376] The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard BLySB Lymphocyte Stimulator level, e.g., in a biological sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed BLySB Lymphocyte Stimulator level compared to the standard level of BLySB Lymphocyte Stimulator is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of BLySB Lymphocyte Stimulator in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0377] In specific embodiments, the presence of a relatively high amount of membrane-bound BLySB Lymphocyte Stimulator in a biological sample is indicative of monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia and/or the severity thereof.

[0378] In other specific embodiments, the presence of a relatively high amount of

BLySB Lymphocyte Stimulator receptor in a biological sample (as determined using antibodies of the invention that bind to soluble BLySB Lymphocyte Stimulator, but do not inhibit BLySB Lymphocyte Stimulator/BLySB Lymphocyte Stimulator receptor binding) is indicative of B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease), and/or the severity thereof.

[0379] In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing Systemic Lupus Erythematosus, comprising: (a) assaying for the level of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard BLySB Lymphocyte Stimulator level, e.g., in a biological sample from a patient without Systemic Lupus Erythematosus, whereby an increase in the assayed BLySB Lymphocyte Stimulator level compared to the standard level of BLySB Lymphocyte Stimulator is indicative of Systemic Lupus Erythematosus.

[0380] In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing a Rheumatoid Arthritis, comprising: (a) assaying for the level of BLySB Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to BLySB Lymphocyte Stimulator; and (b) comparing the level of BLySB Lymphocyte Stimulator with a standard BLySB Lymphocyte Stimulator level, e.g., in a biological sample from a patient without Rheumatoid Arthritis, whereby an increase or decrease in the assayed BLySB Lymphocyte Stimulator level compared to the standard level of BLySB Lymphocyte Stimulator is indicative of Rheumatoid Arthritis.

[0381] The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of BLySB Lymphocyte Stimulator receptor in cells or a tissue sample of an individual using one or more antibodies of the invention that immunospecifically binds only to soluble BLySB Lymphocyte Stimulator, but does not neutralize BLySB Lymphocyte Stimulator /BLySB Lymphocyte Stimulator receptor binding; and (b) comparing the level of BLySB Lymphocyte Stimulator receptor with a standard BLySB Lymphocyte Stimulator receptor level, e.g., in a tissue sample from a patient without the disease or disorder, whereby an

increase or decrease in the assayed BLySB Lymphocyte Stimulator receptor level compared to the standard level of BLySB Lymphocyte Stimulator receptor is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of BLySB Lymphocyte Stimulator receptor in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0382] Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can be used to assay protein levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (*e.g.*, see Jalkanen, *et al.*, J. Cell. Biol. 101:976-985 (1985); Jalkanen, *et al.*, J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, alkaline phosphatase, and horseradish peroxidase; radioisotopes, such as iodine (^{121}I , ^{123}I , ^{125}I , ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{111}In , ^{112}In , $^{113\text{m}}\text{In}$, $^{115\text{m}}\text{In}$), technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , and ^{97}Ru ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0383] One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically binds to BLySB Lymphocyte Stimulator; b) waiting for a time interval following the administering

for permitting the labeled antibody to preferentially concentrate at sites in the subject where BLySB Lymphocyte Stimulator is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled antibody in the subject, such that detection of labeled antibody or fragment thereof above the background level and above or below the level observed in a person without the disease or disorder indicates that the subject has a particular disease or disorder associated with aberrant expression of BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0384] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ⁹⁹Tc. The labeled antibody will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel *et al.*, "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

[0385] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0386] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0387] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the

invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0388] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston *et al.*, U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Immunophenotyping

[0389] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be utilized for immunophenotyping of cell lines and biological samples by their BLySB Lymphocyte Stimulator expression or BLySB Lymphocyte Stimulator receptor expression. Various techniques can be utilized using antibodies, fragments, or variants of the invention to screen for cellular populations (*i.e.*, immune cells, particularly monocytic cells or B-cells) expressing BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor, and include magnetic separation using antibody-coated magnetic beads, “panning” with antibody attached to a solid matrix (*i.e.*, plate), and flow cytometry (see, *e.g.*, U.S. Patent 5,985,660; and Morrison *et al.*, Cell, 96:737-49 (1999)).

[0390] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (*i.e.*, minimal residual disease (MRD) in acute leukemic patients) and “non-self” cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

[0391] In one embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) are used to identify cells of monocytic or B cell origin.

Therapeutic Uses of Antibodies

[0392] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention and nucleic acids encoding antibodies (and anti-idiotypic antibodies) of the invention as described herein. The antibodies of the invention can be used to treat, ameliorate or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of BLySB Lymphocyte Stimulator or BLySB Lymphocyte Stimulator receptor, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant BLySB Lymphocyte Stimulator expression and/or activity or aberrant BLySB Lymphocyte Stimulator receptor expression and/or activity includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0393] Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that function as agonists or antagonists of BLySB Lymphocyte Stimulator, preferably of BLySB Lymphocyte Stimulator-induced signal transduction, can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression, lack of BLySB Lymphocyte Stimulator function, aberrant BLySB Lymphocyte Stimulator receptor expression, or lack of BLySB Lymphocyte Stimulator receptor function. For example, antibodies of the invention which disrupt the interaction between BLySB Lymphocyte Stimulator and its receptor may be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression, excessive BLySB Lymphocyte Stimulator function, aberrant BLySB Lymphocyte Stimulator receptor expression, or excessive of BLySB Lymphocyte Stimulator receptor function. Antibodies of the invention which do not prevent BLySB Lymphocyte Stimulator from binding its receptor

but inhibit or downregulate BLySB Lymphocyte Stimulator-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression, excessive BLySB Lymphocyte Stimulator function, aberrant BLySB Lymphocyte Stimulator receptor expression, or excessive BLySB Lymphocyte Stimulator receptor function. In particular, antibodies of the present invention which prevent BLySB Lymphocyte Stimulator-induced signal transduction by specifically recognizing the unbound BLySB Lymphocyte Stimulator, receptor-bound BLySB Lymphocyte Stimulator or both unbound and receptor-bound BLySB Lymphocyte Stimulator can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression, excessive BLySB Lymphocyte Stimulator function, aberrant BLySB Lymphocyte Stimulator receptor expression, or excessive BLySB Lymphocyte Stimulator receptor function. The ability of an antibody of the invention to inhibit or downregulate BLySB Lymphocyte Stimulator-induced signal transduction may be determined by techniques described herein or otherwise known in the art. For example, BLySB Lymphocyte Stimulator-induced receptor activation and the activation of signaling molecules can be determined by detecting the phosphorylation (*e.g.*, tyrosine or serine/threonine) of the receptor or a signaling molecule by immunoprecipitation followed by western blot analysis (for example, as described herein).

[0394] In a specific embodiment, an antibody of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that inhibits or downregulates BLySB Lymphocyte Stimulator activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to BLySB Lymphocyte Stimulator activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression, excessive BLySB Lymphocyte Stimulator function, aberrant BLySB Lymphocyte Stimulator receptor expression, or excessive BLySB Lymphocyte Stimulator receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments, and/or variants that inhibit or downregulate BLySB Lymphocyte Stimulator

activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to BLySB Lymphocyte Stimulator activity in absence of said antibodies, antibody fragments, and/or antibody variants are administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression, excessive BLySB Lymphocyte Stimulator function, aberrant BLySB Lymphocyte Stimulator receptor expression, or excessive BLySB Lymphocyte Stimulator receptor function.

[0395] Further, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which activate BLySB Lymphocyte Stimulator-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression, lack of BLySB Lymphocyte Stimulator function, aberrant BLySB Lymphocyte Stimulator receptor expression, or lack of BLySB Lymphocyte Stimulator receptor function. These antibodies may potentiate or activate either all or a subset of the biological activities of BLySB Lymphocyte Stimulator-mediated receptor activation, for example, by inducing multimerization of BLySB Lymphocyte Stimulator and/or multimerization of the receptor. The antibodies of the invention may be administered with or without being pre-complexed with BLySB Lymphocyte Stimulator. In a specific embodiment, an antibody of the present invention that increases BLySB Lymphocyte Stimulator activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to BLySB Lymphocyte Stimulator activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression, lack of BLySB Lymphocyte Stimulator function, aberrant BLySB Lymphocyte Stimulator receptor expression, or lack of BLySB Lymphocyte Stimulator receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments and/or antibody variants that increase

BLySB Lymphocyte Stimulator activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to BLySB Lymphocyte Stimulator activity in absence of the said antibodies or antibody fragments and/or antibody variants is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression or lack of BLySB Lymphocyte Stimulator function or aberrant BLySB Lymphocyte Stimulator receptor expression or lack of BLySB Lymphocyte Stimulator receptor function.

[0396] One or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator may be used locally or systemically in the body as a therapeutic. The antibodies of this invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, *e.g.*, IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0397] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be administered alone or in combination with other types of treatments (*e.g.*, radiation therapy, chemotherapy, hormonal therapy, immunotherapy, anti-tumor agents, anti-angiogenesis and anti-inflammatory agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments, or variants, (*e.g.*, derivatives), or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0398] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLySB Lymphocyte Stimulator, or polynucleotides encoding antibodies that immunospecifically bind to BLySB Lymphocyte Stimulator, for both immunoassays

directed to and therapy of disorders related to BLySB Lymphocyte Stimulator polynucleotides or polypeptides, including fragments thereof. Such antibodies will preferably have an affinity for BLySB Lymphocyte Stimulator and/or BLySB Lymphocyte Stimulator fragments. Preferred binding affinities include those with a dissociation constant or K_D less than or equal to 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, or 10^{-5} M. More preferably, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, or 10^{-8} M. Even more preferably, antibodies of the invention bind BLySB Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. The invention encompasses antibodies that bind BLySB Lymphocyte Stimulator polypeptides with a dissociation constant or K_D that is within any one of the ranges that are between each of the individual recited values.

[0399] In a preferred embodiment, antibodies of the invention neutralize BLySB Lymphocyte Stimulator activity. In another preferred embodiment, antibodies of the invention inhibit B cell proliferation.

[0400] In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of the soluble form of BLySB Lymphocyte Stimulator to a BLySB Lymphocyte Stimulator receptor. In another preferred embodiment antibodies of the invention inhibit or reduce B cell proliferation induced by the soluble form of BLySB Lymphocyte Stimulator. In another preferred embodiment antibodies of the invention inhibit or reduce immunoglobulin production induced by the soluble form of BLySB Lymphocyte Stimulator.

[0401] In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of membrane-bound BLySB Lymphocyte Stimulator to a BLySB Lymphocyte Stimulator receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by the membrane-bound form of BLySB Lymphocyte Stimulator. In another preferred embodiment, antibodies of

the invention inhibit or reduce immunoglobulin production induced by the membrane bound form of BLySB Lymphocyte Stimulator.

[0402] In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of both the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator to a BLySB Lymphocyte Stimulator receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by either or both forms of BLySB Lymphocyte Stimulator. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by either or both forms of BLySB Lymphocyte Stimulator.

[0403] In one embodiment, the invention provides a method of delivering antibody conjugates of the invention to targeted cells, such as, for example, monocytic cells expressing the membrane-bound form of BLySB Lymphocyte Stimulator, or B cells expressing a BLySB Lymphocyte Stimulator receptor.

[0404] In one embodiment, the invention provides a method for the specific delivery of antibodies and antibody conjugates of the invention to cells by administering molecules of the invention that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0405] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs). In a specific embodiment, the invention provides a method for the specific destruction of cells of monocytic lineage (e.g., monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that immunospecifically bind the membrane-bound form of BLySB Lymphocyte Stimulator. In another specific embodiment, the invention provides a method for the specific destruction of cells of B cell

lineage (e.g., B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that bind soluble BLySB Lymphocyte Stimulator, but do not inhibit BLySB Lymphocyte Stimulator binding to a BLySB Lymphocyte Stimulator receptor on B cells.

[0406] In another preferred embodiment antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the soluble form of BLySB Lymphocyte Stimulator. In another preferred embodiment, antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the membrane or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production induced by the soluble form of BLySB Lymphocyte Stimulator. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production induced by the membrane bound or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production in response to T cell dependent immunogens. In another preferred embodiment antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance immunoglobulin production in response to T cell independent immunogens.

[0407] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate immune disorders. Immune disorders include, but are not limited to, autoimmune disorders (e.g., arthritis, graft rejection, Hashimoto's thyroiditis, insulin-dependent diabetes, lupus, idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis), elective IgA deficiency, ataxia-telangiectasia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, idiopathic hyper-eosinophilic syndrome, monocytic leukemoid reaction, monocytic leukocytosis, monocytic leukopenia, monocytopenia, monocytosis, and graft or transplant rejection.

[0408] As discussed herein, antibodies and antibody compositions of the

invention, may be used to treat, prevent, ameliorate, diagnose or prognose various immune system-related disorders and/or conditions associated with these disorders, in mammals, preferably humans. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of antibody and antibody compositions of the invention that can inhibit an immune response, particularly the proliferation of B cells and/or the production of immunoglobulins, may be an effective therapy in treating and/or preventing autoimmune disorders. Thus, in preferred embodiments, antibodies and antibody compositions of the invention are used to treat, prevent, ameliorate, diagnose and/or prognose an autoimmune disorder, or condition(s) associated with such disorder.

[0409] Autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

[0410] Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis) (often characterized, e.g., by cell-mediated and humoral thyroid cytotoxicity), systemic lupus erythematosus (often characterized, e.g., by circulating and locally generated immune complexes), discoid lupus, Goodpasture's syndrome (often characterized, e.g., by anti-basement membrane antibodies), Pemphigus (often characterized, e.g., by epidermal acantholytic antibodies), Receptor autoimmunities such as, for example, (a) Graves'

Disease (often characterized, e.g., by TSH receptor antibodies), (b) Myasthenia Gravis (often characterized, e.g., by acetylcholine receptor antibodies), and (c) insulin resistance (often characterized, e.g., by insulin receptor antibodies), autoimmune hemolytic anemia (often characterized, e.g., by phagocytosis of antibody-sensitized RBCs), autoimmune thrombocytopenic purpura (often characterized, e.g., by phagocytosis of antibody-sensitized platelets).

[0411] Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, rheumatoid arthritis (often characterized, e.g., by immune complexes in joints), scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis/dermatomyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes) such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjögren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies), chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondrial antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM

antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), inflammatory myopathies, and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0412] In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, a member of the group: autoimmune hemolytic anemia, as primary glomerulonephritis, IgA glomerulonephritis, Goodpasture's syndrome, idiopathic thrombocytopenia, Multiple Sclerosis, Myasthenia Gravis, Pemphigus, polymyositis/dermatomyositis, relapsing polychondritis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Uveitis, vasculitis, and primary biliary cirrhosis.

[0413] In another preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, an immune based-rheumatologic disease, such as, for example, SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), polymyositis/ dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder.

[0414] In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, rheumatoid arthritis and/or medical conditions associated therewith.

[0415] For example, an antibody, or antibodies, of the present invention are used to treat patients with clinical diagnosis of rheumatoid arthritis (RA). The patient treated preferably will not have a B cell malignancy. Moreover, the patient is optionally further treated with any one or more agents employed for treating RA such as salicylate; nonsteroidal anti-inflammatory drugs such as indomethacin, phenylbutazone, phenylacetic acid derivatives (e.g. ibuprofen and fenoprofen), naphthalene acetic acids (naproxen), pyrrolealkanoic acid (tometin), indoleacetic acids (sulindac), halogenated anthranilic acid (meclofenamate sodium), piroxicam, zomepirac and diflunisal; antimalarials such as chloroquine; gold salts; penicillamine; or immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages. Preferably

however, the patient is only treated with an antibody, or antibodies, of the present invention. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. The primary response is determined by the Paulus index (Paulus et al. *Athritis Rheum.* 33:477-484 (1990)), *i.e.* improvement in morning stiffness, number of painful and inflamed joints, erythrocyte sedimentation (ESR), and at least a 2-point improvement on a 5-point scale of disease severity assessed by patient and by physician. Administration of an antibody, or antibodies, of the present invention will alleviate one or more of the symptoms of RA in the patient treated as described above.

[0416] In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, lupus and/or medical conditions associated therewith. Lupus-associated conditions that may be treated, prevented, ameliorated, prognosed and/or diagnosed with the antibodies and antibody compositions of the invention include, but are not limited to, hematologic disorders (e.g., hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia), immunologic disorders (e.g., anti-DNA antibodies, and anti-Sm antibodies), rashes, photosensitivity, oral ulcers, arthritis, fever, fatigue, weight loss, serositis (e.g., pleuritis (pleurisy)), renal disorders (e.g., nephritis), neurological disorders (e.g., seizures, peripheral neuropathy, CNS related disorders), gastrointestinal disorders, Raynaud phenomenon, and pericarditis. In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognose, renal disorders associated with systemic lupus erythematosus. In a most preferred embodiment, therapeutic and pharmaceutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognose, nephritis associated with systemic lupus erythematosus. In another most preferred embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate lupus or glomerular nephritis.

[0417] In a further specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent hemolytic anemia. For example, patients diagnosed with autoimmune hemolytic anemia (AIHA), *e.g.*, cryoglobulinemia or Coombs positive anemia, are treated with an antibody, or antibodies, of the present invention. AIHA is an acquired hemolytic anemia due to auto-antibodies that react with the patient's

red blood cells. The patient treated preferably will not have a B cell malignancy. Further adjunct therapies (such as glucocorticoids, prednisone, azathioprine, cyclophosphamide, vinca-laden platelets or Danazol) may be combined with the antibody therapy, but preferably the patient is treated with an antibody, or antibodies, of the present invention as a single-agent throughout the course of therapy. Antibodies of the present invention are administered to the hemolytic anemia patient according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. Overall response rate is determined based upon an improvement in blood counts, decreased requirement for transfusions, improved hemoglobin levels and/or a decrease in the evidence of hemolysis as determined by standard chemical parameters. Administration of an antibody, or antibodies of the present invention will improve any one or more of the symptoms of hemolytic anemia in the patient treated as described above. For example, the patient treated as described above will show an increase in hemoglobin and an improvement in chemical parameters of hemolysis or return to normal as measured by serum lactic dehydrogenase and/or bilirubin.

[0418] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Sjögren's Syndrome and/or medical conditions associated therewith.

[0419] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, HIV infection and/or medical conditions associated therewith (e.g. AIDS).

[0420] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Myasthenia gravis and/or medical conditions associated therewith.

[0421] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, IgA nephropathy and/or medical conditions associated therewith.

[0422] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, hemolytic anemia and/or medical conditions associated therewith.

[0423] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, thyroiditis and/or medical conditions associated therewith.

[0424] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Goodpasture's Syndrome and/or medical conditions associated therewith.

[0425] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple sclerosis and/or medical conditions associated therewith.

[0426] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, chronic lymphocytic leukemia (CLL) and/or medical conditions associated therewith.

[0427] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple myeloma and/or medical conditions associated therewith.

[0428] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Non-Hodgkin's lymphoma and/or medical conditions associated therewith.

[0429] In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Hodgkin's disease and/or medical conditions associated therewith.

[0430] In another specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent adult immune thrombocytopenic purpura. Adult immune thrombocytopenic purpura (ITP) is a relatively rare hematologic disorder that constitutes the most common of the immune-mediated cytopenias. The disease typically presents with severe thrombocytopenia that may be associated with acute hemorrhage in the presence of normal to increased megakaryocytes in the bone marrow. Most patients with ITP have an IgG antibody directed against target antigens on the outer surface of the platelet membrane, resulting in platelet sequestration in the spleen and accelerated reticuloendothelial destruction of platelets (Bussell, J.B. Hematol. Oncol. Clin. North Am. (4):179 (1990)). A number of therapeutic interventions have been shown to be effective in the treatment of ITP. Steroids are generally considered first-line therapy, after

which most patients are candidates for intravenous immunoglobulin (IVIG), splenectomy, or other medical therapies including vincristine or immunosuppressive/cytotoxic agents. Up to 80% of patients with ITP initially respond to a course of steroids, but far fewer have complete and lasting remissions. Splenectomy has been recommended as standard second-line therapy for steroid failures, and leads to prolonged remission in nearly 60% of cases yet may result in reduced immunity to infection. Splenectomy is a major surgical procedure that may be associated with substantial morbidity (15%) and mortality (2%). IVIG has also been used as second line medical therapy, although only a small proportion of adult patients with ITP achieve remission. Therapeutic options that would interfere with the production of autoantibodies by activated B cells without the associated morbidities that occur with corticosteroids and/or splenectomy would provide an important treatment approach for a proportion of patients with ITP. Patients with clinical diagnosis of ITP are treated with an antibody, or antibodies of the present invention, optionally in combination with steroid therapy. The patient treated will not have a B cell malignancy. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described *infra*, which may be readily determined by one of ordinary skill in the art. Overall patient response rate is determined based upon a platelet count determined on two consecutive occasions two weeks apart following treatments as described above. See, George et al. "Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology", Blood 88:3-40 (1996), expressly incorporated herein by reference.

[0431] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate an IgE-mediated allergic reaction or histamine-mediated allergic reaction. Examples of allergic reactions include, but are not limited to, asthma, rhinitis, eczema, chronic urticaria, and atopic dermatitis. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent, or ameliorate anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate or modulate inflammation or an inflammatory disorder. Examples of chronic and acute inflammatory disorders that may be treated prevented or ameliorated with the therapeutic and pharmaceutical compositions

of the invention include, but are not limited to, chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, Crohn's disease, inflammatory bowel disease, chronic and acute inflammatory pulmonary diseases, bacterial infection, psoriasis, septicemia, cerebral malaria, arthritis, gastroenteritis, and glomerular nephritis.

[0432] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate ischemia and arteriosclerosis. Examples of such disorders include, but are not limited to, reperfusion damage (e.g., in the heart and/or brain) and cardiac hypertrophy.

[0433] Therapeutic or pharmaceutical compositions of the invention, may also be administered to modulate blood clotting and to treat or prevent blood clotting disorders, such as, for example, antibody-mediated thrombosis (i.e., antiphospholipid antibody syndrome (APS)). For example, therapeutic or pharmaceutical compositions of the invention, may inhibit the proliferation and differentiation of cells involved in producing anticardiolipin antibodies. These compositions of the invention can be used to treat, prevent, ameliorate, diagnose, and/or prognose thrombotic related events including, but not limited to, stroke (and recurrent stroke), heart attack, deep vein thrombosis, pulmonary embolism, myocardial infarction, coronary artery disease (e.g., antibody-mediated coronary artery disease), thrombosis, graft reocclusion following cardiovascular surgery (e.g., coronary arterial bypass grafts, recurrent fetal loss, and recurrent cardiovascular thromboembolic events).

[0434] Therapeutic or pharmaceutical compositions of the invention, may also be administered to treat, prevent, or ameliorate organ rejection or graft-versus-host disease (GVHD) and/or conditions associated therewith. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of antibodies of the invention, that inhibit an immune response, may be an effective therapy in preventing organ rejection or GVHD.

[0435] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate a disease or disorder diseases associated with increased apoptosis including, but not limited to, AIDS, neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration), myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate bone marrow failure, for example, aplastic anemia and myelodysplastic syndrome.

[0436] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate growth, progression, and/or metastases of malignancies and proliferative disorders associated with increased cell survival, or the inhibition of apoptosis. Examples of such disorders, include, but are not limited to, leukemia (*e.g.*, acute leukemia such as acute lymphocytic leukemia and acute myelocytic leukemia), neoplasms, tumors (*e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma), heavy chain disease, metastases, or any disease or disorder characterized by uncontrolled cell growth.

[0437] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by

hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies).

[0438] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, therapeutic or pharmaceutical compositions of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, COVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii.

[0439] Therapeutic or pharmaceutical compositions of the invention of the invention thereof, may be used to diagnose, prognose, treat or prevent one or more of the following diseases or disorders, or conditions associated therewith: primary immunodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, bone marrow transplant (e.g., recent bone marrow transplant in adults or children), chronic B-cell lymphocytic leukemia, HIV infection (e.g., adult or pediatric HIV infection), chronic inflammatory demyelinating polyneuropathy, and post-transfusion purpura.

[0440] Additionally, therapeutic or pharmaceutical compositions of the invention may be used to diagnose, prognose, treat or prevent one or more of the following diseases, disorders, or conditions associated therewith, Guillain-Barre syndrome, anemia (e.g., anemia associated with parvovirus B19, patients with stable multiple myeloma who are at high risk for infection (e.g., recurrent infection), autoimmune hemolytic anemia (e.g., warm-type autoimmune hemolytic anemia), thrombocytopenia (e.g., neonatal thrombocytopenia), and immune-mediated neutropenia), transplantation (e.g., cytomegalovirus (CMV)-negative recipients of CMV-positive organs), hypogammaglobulinemia (e.g., hypogammaglobulinemic neonates with risk factor for infection or morbidity), epilepsy (e.g., intractable epilepsy), systemic vasculitic syndromes, myasthenia gravis (e.g., decompensation in myasthenia gravis),

dermatomyositis, and polymyositis.

[0441] Additional preferred embodiments of the invention include, but are not limited to, the use of therapeutic or pharmaceutical compositions of the invention in the following applications:

[0442] Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response. In a specific nonexclusive embodiment, therapeutic or pharmaceutical compositions of the invention are administered to boost the immune system to produce increased quantities of IgG. In another specific nonexclusive embodiment, antibodies of the are administered to boost the immune system to produce increased quantities of IgA. In another specific nonexclusive embodiment antibodies of the invention are administered to boost the immune system to produce increased quantities of IgM.

[0443] Administration to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741).

[0444] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a vaccine adjuvant that enhances immune responsiveness to specific antigen. In a specific embodiment, the vaccine is an antibody described herein. In another specific embodiment, the vaccine adjuvant is a polynucleotide described herein (e.g., an antibody polynucleotide genetic vaccine adjuvant). As discussed herein, therapeutic or pharmaceutical compositions of the invention may be administered using techniques known in the art, including but not limited to, liposomal delivery, recombinant vector delivery, injection of naked DNA, and gene gun delivery.

[0445] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance tumor-specific immune responses.

[0446] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include, but are not limited to, virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to the HIV gp120 antigen.

[0447] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella* spp., Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and *Plasmodium* (malaria).

[0448] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention

as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria).

[0449] In a specific embodiment, compositions of the invention may be administered to patients as vaccine adjuvants. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from an immune-deficiency. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from HIV.

[0450] In a specific embodiment, compositions of the invention may be used to increase or enhance antigen-specific antibody responses to standard and experimental vaccines. In a specific embodiment, compositions of the invention may be used to enhance seroconversion in patients treated with standard and experimental vaccines. In another specific embodiment, compositions of the invention may be used to increase the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination.

[0451] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of BLySB Lymphocyte Stimulator to a BLySB Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0452] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of BLySB Lymphocyte Stimulator to BLySB Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies)

increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0453] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of BLySB Lymphocyte Stimulator to a BLySB Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0454] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell responsiveness to pathogens.

[0455] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[0456] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to induce higher affinity antibodies.

[0457] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to increase serum immunoglobulin concentrations.

[0458] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to accelerate recovery of immunocompromised individuals.

[0459] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among aged populations.

[0460] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be

administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[0461] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy. B cell immunodeficiencies that may be ameliorated or treated by administering the antibodies and/or compositions of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

[0462] In a specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate selective IgA deficiency.

[0463] In another specific embodiment, antibodies and/or compositions of the

invention are administered to treat or ameliorate ataxia-telangiectasia.

[0464] In another specific embodiment antibodies and/or compositions of the invention are administered to treat or ameliorate common variable immunodeficiency.

[0465] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked agammaglobulinemia.

[0466] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate severe combined immunodeficiency (SCID).

[0467] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate Wiskott-Aldrich syndrome.

[0468] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked Ig deficiency with hyper IgM.

[0469] As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0470] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

[0471] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a regulator of antigen presentation by monocytes, dendritic cells, T cells and/or B-cells. In one embodiment, antibody polypeptides or polynucleotides enhance antigen presentation or antagonize antigen presentation in vitro or in vivo. Moreover, in related embodiments, this enhancement or antagonization of antigen presentation may be useful in anti-tumor treatment or to modulate the immune system.

[0472] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a mediator of mucosal immune responses. The expression of BLySB Lymphocyte Stimulator on monocytes, the expression of BLySB Lymphocyte Stimulator receptor on B cells, and the responsiveness of B cells to BLySB Lymphocyte Stimulator suggests that it may be involved in exchange of signals between B cells and monocytes or their differentiated progeny. This activity is in many ways analogous to the CD40-CD154 signalling between B cells and T cells. Anti-BLySB Lymphocyte Stimulator antibodies and compositions of the invention may therefore be good regulators of T cell independent immune responses to environmental pathogens. In particular, the unconventional B cell populations (CD5+) that are associated with mucosal sites and responsible for much of the innate immunity in humans may respond to antibodies or compositions of the invention thereby enhancing or inhibiting individual's immune status.

[0473] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0474] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly, their susceptibility profile would likely change.

[0475] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a monocyte cell specific binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

[0476] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a B cell specific binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

[0477] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting monocytic cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as

described herein) to afford a means of detection.

[0478] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting B-lineage cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

[0479] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable immunodeficiency.

[0480] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a monocyte selection device the function of which is to isolate monocytes from a heterogeneous mixture of cell types. Antibodies of the invention could be coupled to a solid support to which monocytes would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

[0481] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a B cell selection device the function of which is to isolate B cells from a heterogeneous mixture of cell types. Antibodies of the invention (that do not inhibit BLySB Lymphocyte Stimulator/BLySB Lymphocyte Stimulator Receptor interaction) binding soluble BLySB Lymphocyte Stimulator could be coupled to a solid support to which B cells would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

[0482] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

[0483] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

[0484] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an antigen for the generation of antibodies to inhibit or enhance

BLySB Lymphocyte Stimulator mediated responses.

[0485] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0486] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recovery.

[0487] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of regulating secreted cytokines that are elicited by BLySB Lymphocyte Stimulator and/or BLySB Lymphocyte Stimulator receptor.

[0488] Antibody polypeptides or polynucleotides of the invention may be used to modulate IgE concentrations in vitro or in vivo.

[0489] Additionally, antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

[0490] In a specific embodiment, antibody polypeptides or polynucleotides of the invention, are administered to treat, prevent, diagnose, and/or ameliorate selective IgA deficiency.

[0491] In another specific embodiment antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate ataxia-telangiectasia.

[0492] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate common variable immunodeficiency.

[0493] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked agammaglobulinemia.

[0494] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate severe combined immunodeficiency (SCID).

[0495] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate Wiskott-

Aldrich syndrome.

[0496] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM. In a specific embodiment antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM.

[0497] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, and/or diagnose chronic myelogenous leukemia, acute myelogenous leukemia, leukemia, hystiocytic leukemia, monocytic leukemia (e.g., acute monocytic leukemia), leukemic reticulosis, Shilling Type monocytic leukemia, and/or other leukemias derived from monocytes and/or monocytic cells and/or tissues.

[0498] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukemoid reaction, as seen, for example, with tuberculosis.

[0499] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukocytosis, monocytic leukopenia, monocytopenia, and/or monocytosis.

[0500] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose monocyte disorders and/or diseases, and/or conditions associated therewith.

[0501] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose primary B lymphocyte disorders and/or diseases, and/or conditions associated therewith. In one embodiment, such primary B lymphocyte disorders, diseases, and/or conditions are characterized by a complete or partial loss of humoral immunity. Primary B lymphocyte disorders, diseases, and/or conditions associated therewith that are characterized by a complete or partial loss of humoral immunity and that may be prevented, treated, detected and/or diagnosed with compositions of the invention include, but are not limited to, X-Linked Agammaglobulinemia (XLA), severe combined immunodeficiency disease (SCID), and selective IgA deficiency.

[0502] In a preferred embodiment antibody polypeptides or polynucleotides of the

invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with any one or more of the various mucous membranes of the body. Such diseases or disorders include, but are not limited to, for example, mucositis, mucoclasia, mucocolitis, mucocutaneous leishmaniasis (such as, for example, American leishmaniasis, leishmaniasis americana, nasopharyngeal leishmaniasis, and New World leishmaniasis), mucocutaneous lymph node syndrome (for example, Kawasaki disease), mucoenteritis, mucoepidermoid carcinoma, mucoepidermoid tumor, mucoepithelial dysplasia, mucoid adenocarcinoma, mucoid degeneration, myxoid degeneration; myxomatous degeneration; myxomatosis, mucoid medial degeneration (for example, cystic medial necrosis), mucolipidosis (including, for example, mucolipidosis I, mucolipidosis II, mucolipidosis III, and mucolipidosis IV), mucolysis disorders, mucomembranous enteritis, mucoenteritis, mucopolysaccharidosis (such as, for example, type I mucopolysaccharidosis (i.e., Hurler's syndrome), type IS mucopolysaccharidosis (i.e., Scheie's syndrome or type V mucopolysaccharidosis), type II mucopolysaccharidosis (i.e., Hunter's syndrome), type III mucopolysaccharidosis (i.e., Sanfilippo's syndrome), type IV mucopolysaccharidosis (i.e., Morquio's syndrome), type VI mucopolysaccharidosis (i.e., Maroteaux-Lamy syndrome), type VII mucopolysaccharidosis (i.e., mucopolysaccharidosis due to beta-glucuronidase deficiency), and mucosulfatidosis), mucopolysacchariduria, mucopurulent conjunctivitis, mucopus, mucormycosis (i.e., zygomycosis), mucosal disease (i.e., bovine virus diarrhea), mucous colitis (such as, for example, mucocolitis and myxomembranous colitis), and mucoviscidosis (such as, for example, cystic fibrosis, cystic fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocystic disease of the pancreas, mucoviscidosis, and viscidosis). In a highly preferred embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose mucositis, especially as associated with chemotherapy.

[0503] In a preferred embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with sinusitis.

[0504] An additional condition, disease or symptom that can be treated, prevented, and/or diagnosed by antibody polypeptides or polynucleotides of the invention is osteomyelitis.

[0505] An additional condition, disease or symptom that can be treated, prevented, and/or diagnosed by antibody polypeptides or polynucleotides of the invention is endocarditis.

[0506] All of the above described applications as they may apply to veterinary medicine.

[0507] Antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose diseases and disorders of the pulmonary system (e.g., bronchi such as, for example, sinopulmonary and bronchial infections and conditions associated with such diseases and disorders and other respiratory diseases and disorders. In specific embodiments, such diseases and disorders include, but are not limited to, bronchial adenoma, bronchial asthma, pneumonia (such as, e.g., bronchial pneumonia, bronchopneumonia, and tuberculous bronchopneumonia), chronic obstructive pulmonary disease (COPD), bronchial polyps, bronchiectasia (such as, e.g., bronchiectasia sicca, cylindrical bronchiectasis, and saccular bronchiectasis), bronchiolar adenocarcinoma, bronchiolar carcinoma, bronchiolitis (such as, e.g., exudative bronchiolitis, bronchiolitis fibrosa obliterans, and proliferative bronchiolitis), bronchiolo-alveolar carcinoma, bronchitic asthma, bronchitis (such as, e.g., asthmatic bronchitis, Castellani's bronchitis, chronic bronchitis, croupous bronchitis, fibrinous bronchitis, hemorrhagic bronchitis, infectious avian bronchitis, obliterative bronchitis, plastic bronchitis, pseudomembranous bronchitis, putrid bronchitis, and verminous bronchitis), bronchocentric granulomatosis, bronchoedema, bronchoesophageal fistula, bronchogenic carcinoma, bronchogenic cyst, broncholithiasis, bronchomalacia, bronchomycosis (such as, e.g., bronchopulmonary aspergillosis), bronchopulmonary spirochetosis, hemorrhagic bronchitis, bronchorrhea, bronchospasm, bronchostaxis, bronchostenosis, Biot's respiration, bronchial respiration, Kussmaul respiration, Kussmaul-Kien respiration, respiratory acidosis, respiratory alkalosis, respiratory distress syndrome of the newborn, respiratory insufficiency, respiratory scleroma, respiratory syncytial virus, and the like.

[0508] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose chronic obstructive pulmonary disease (COPD).

[0509] In another embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose fibroses and conditions associated

with fibroses, including, but not limited to, cystic fibrosis (including such fibroses as cystic fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocystic disease of the pancreas, mucoviscidosis, and viscidosis), endomyocardial fibrosis, idiopathic retroperitoneal fibrosis, leptomeningeal fibrosis, mediastinal fibrosis, nodular subepidermal fibrosis, pericentral fibrosis, perimuscular fibrosis, pipestem fibrosis, replacement fibrosis, subadventitial fibrosis, and Symmers' clay pipestem fibrosis.

[0510] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate infectious diseases. Infectious diseases include diseases associated with yeast, fungal, viral and bacterial infections. Viruses causing viral infections which can be treated or prevented in accordance with this invention include, but are not limited to, retroviruses (*e.g.*, human T-cell lymphotropic virus (HTLV) types I and II and human immunodeficiency virus (HIV)), herpes viruses (*e.g.*, herpes simplex virus (HSV) types I and II, Epstein-Barr virus, HHV6-HHV8, and cytomegalovirus), arenaviruses (*e.g.*, lassa fever virus), paramyxoviruses (*e.g.*, morbillivirus virus, human respiratory syncytial virus, mumps, and pneumovirus), adenoviruses, bunyaviruses (*e.g.*, hantavirus), coronaviruses, filoviruses (*e.g.*, Ebola virus), flaviviruses (*e.g.*, hepatitis C virus (HCV), yellow fever virus, and Japanese encephalitis virus), hepadnaviruses (*e.g.*, hepatitis B viruses (HBV)), orthomyxoviruses (*e.g.*, influenza viruses A, B and C), papovaviruses (*e.g.*, papillomaviruses), picornaviruses (*e.g.*, rhinoviruses, enteroviruses and hepatitis A viruses), poxviruses, reoviruses (*e.g.*, rotaviruses), togaviruses (*e.g.*, rubella virus), rhabdoviruses (*e.g.*, rabies virus). Microbial pathogens causing bacterial infections include, but are not limited to, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium perfringens*, *Clostridium tetani*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Klebsiella rhinoscleromatis*, *Staphylococcus aureus*, *Vibrio cholerae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Campylobacter* (*Vibrio*) *fetus*, *Campylobacter jejuni*, *Aeromonas hydrophila*, *Bacillus cereus*, *Edwardsiella tarda*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Salmonella typhimurium*, *Treponema pallidum*, *Treponema pertenue*, *Treponema carateneum*, *Borrelia vincentii*, *Borrelia burgdorferi*, *Leptospira icterohemorrhagiae*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*,

Pneumocystis carinii, *Francisella tularensis*, *Brucella abortus*, *Brucella suis*, *Brucella melitensis*, *Mycoplasma spp.*, *Rickettsia prowazeki*, *Rickettsia tsutsugumushi*, *Chlamydia spp.*, and *Helicobacter pylori*.

Gene Therapy

[0511] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of BLySB Lymphocyte Stimulator and/or its receptor, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0512] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0513] For general reviews of the methods of gene therapy, see Goldspiel *et al.*, Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[0514] In a preferred aspect, a composition of the invention comprises, or alternatively consists of, nucleic acids encoding an antibody, said nucleic acids being part of an expression vector that expresses the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for

intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra *et al.*, Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is an scFv; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments or variants thereof, of an antibody.

[0515] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

[0516] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, *e.g.*, by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, *e.g.*, by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, *e.g.*, PCT Publications WO 92/06 180; WO 92/22635; W092/203 16; W093/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra *et al.*, Nature 342:435-438 (1989)).

[0517] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention or fragments or variants thereof are used. For example, a retroviral vector can be used (see Miller *et al.*, Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen *et al.*, Biotherapy 6:29 1-302 (1994), which describes the use of a retroviral vector to deliver the *mdr 1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes *et al.*, J. Clin. Invest. 93:644-651(1994); Klein *et al.*, Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[0518] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout *et al.*, Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld *et al.*, Science 252:431-434 (1991); Rosenfeld *et al.*, Cell 68:143- 155 (1992); Mastrangeli *et al.*, J. Clin. Invest. 91:225-234 (1993); PCT Publication W094/12649; and Wang, *et al.*, Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0519] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh *et al.*, Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0520] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated

transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0521] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, *e.g.*, Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen *et al.*, *Meth. Enzymol.* 217:618-644 (1993); *Clin. Pharma. Ther.* 29:69-92m (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0522] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (*e.g.*, hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0523] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0524] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0525] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody or fragment thereof are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[0526] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Utility of a Composition

[0527] The compounds of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, *in vitro* assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if an antibody or composition of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested in *in vitro* assays and animal model systems prior to administration to humans.

[0528] Antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, chicken, cows, monkeys, and rabbits. For *in vivo* testing of an antibody or composition's toxicity any animal model system known in the art may be used.

[0529] Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of an antibody or composition of the invention to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, or to prevent, ameliorate or alleviate the symptoms of disease a progression. The treatment is considered therapeutic if there is, for example, a reduction in viral load, amelioration of one or more symptoms, or a decrease in mortality and/or morbidity following administration of an antibody or composition of the invention.

[0530] Antibodies or compositions of the invention can be tested for the ability to induce the expression of cytokines such as IFN- γ , by contacting cells, preferably human cells, with an antibody or composition of the invention or a control antibody or control composition and determining the ability of the antibody or composition of the invention to induce one or more cytokines. Techniques known to those of skill in the art can be used to measure the level of expression of cytokines. For example, the level of expression of cytokines can be measured by analyzing the level of RNA of cytokines by, for example, RT-PCR and Northern blot analysis, and by analyzing the level of cytokines by, for example, immunoprecipitation followed by western blot analysis and ELISA. In a preferred embodiment, a compound of the invention is tested for its ability to induce the expression of IFN- γ .

[0531] Antibodies or compositions of the invention can be tested for their ability to modulate the biological activity of immune cells by contacting immune cells, preferably human immune cells (*e.g.*, T-cells, B-cells, and Natural Killer cells), with an antibody or composition of the invention or a control compound and determining the ability of the antibody or composition of the invention to modulate (*i.e.*, increase or decrease) the biological activity of immune cells. The ability of an antibody or composition of the invention to modulate the biological activity of immune cells can be assessed by detecting the expression of antigens, detecting the proliferation of immune cells (*i.e.*, B-cell proliferation), detecting the activation of signaling molecules, detecting the effector function of immune cells, or detecting the differentiation of immune cells. Techniques known to those of skill in the art can be used for measuring these activities. For example, cellular proliferation can be assayed by ^3H -thymidine incorporation assays and trypan blue cell counts. Antigen expression can be assayed, for example, by immunoassays including, but not limited to, competitive and non-competitive assay systems using

techniques such as western blots, immunohistochemistry radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays and FACS analysis. The activation of signaling molecules can be assayed, for example, by kinase assays and electrophoretic shift assays (EMSAs). In a preferred embodiment, the ability of an antibody or composition of the invention to induce B-cell proliferation is measured. In another preferred embodiment, the ability of an antibody or composition of the invention to modulate immunoglobulin expression is measured.

[0532] Antibodies or compositions of the invention can be tested for their ability to reduce tumor formation in *in vitro*, *ex vivo* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to inhibit viral replication or reduce viral load in *in vitro* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to reduce bacterial numbers in *in vitro* and *in vivo* assays known to those of skill in the art. Antibodies or compositions of the invention can also be tested for their ability to alleviate one or more symptoms associated with cancer, an immune disorder (*e.g.*, an inflammatory disease), a neurological disorder or an infectious disease. Antibodies or compositions of the invention can also be tested for their ability to decrease the time course of the infectious disease. Further, antibodies or compositions of the invention can be tested for their ability to increase the survival period of animals suffering from disease or disorder, including cancer, an immune disorder or an infectious disease. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention *in vivo*.

Therapeutic/Prophylactic Compositions and Administration

[0533] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of antibody (or fragment or variant thereof) or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, an antibody or fragment or variant thereof is substantially purified (*i.e.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to, animals

such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

[0534] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0535] Various delivery systems are known and can be used to administer antibody or fragment or variant thereof of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or antibody fragment, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0536] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0537] In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat *et al.*, in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

[0538] In yet another embodiment, the composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald *et al.*, Surgery 88:507 (1980); Saudek *et al.*, N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy *et al.*, Science 228:190 (1985); During *et al.*, Ann. Neurol. 25:351 (1989); Howard *et al.*, J. Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, *i.e.*, the brain, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

[0539] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0540] In a specific embodiment where the composition of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see *e.g.*, Joliot *et al.*, Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0541] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an antibody or a fragment thereof, and a pharmaceutically acceptable carrier. In a specific embodiment, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in “Remington's Pharmaceutical Sciences” by E.W. Martin. Such compositions will contain a therapeutically effective amount of the antibody or fragment thereof, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0542] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at

the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0543] The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0544] The amount of the composition of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0545] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of therapeutic or pharmaceutical compositions of the invention may be reduced by enhancing uptake and tissue penetration (*e.g.*, into the brain) of the antibodies by modifications such as, for example, lipidation.

[0546] The antibodies and antibody compositions of the invention may be administered alone or in combination with other adjuvants. Adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with alum. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis, and/or PNEUMOVAX-23™. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0547] In another specific embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated therewith. In one embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose any Gram positive bacterial infection and/or any disease, disorder, and/or condition associated therewith. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more

members of the genus *Enterococcus* and/or the genus *Streptococcus*. In another embodiment, antibody and antibody compositions of the invention are used in any combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the Group B streptococci. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with *Streptococcus pneumoniae*.

[0548] The antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic agents, including but not limited to, chemotherapeutic agents, antibiotics, antivirals, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents and cytokines. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0549] In one embodiment, the antibody and antibody compositions of the invention are administered in combination with other members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), TRAIL, AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190 (1998)), endokine-alpha (International Publication No. WO 98/07880), Neutrokine-alpha (Internatioanl Application Publication No. WO 98/18921), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International

Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[0550] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVREND™), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

[0551] In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-angiogenic agent(s). Anti-angiogenic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0552] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0553] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0554] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include

tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0555] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., *Cancer Res.* 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., *J. Bio. Chem.* 267:17321-17326, 1992); Chymostatin (Tomkinson et al., *Biochem J.* 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., *Nature* 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, *J. Clin. Invest.* 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., *J. Biol. Chem.* 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., *Agents Actions* 36:312-316, 1992); and metalloproteinase inhibitors such as BB94.

[0556] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine

(Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

[0557] Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, EMD-121974 (Merck KgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-

alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

[0558] In particular embodiments, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

[0559] In a particular embodiment, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

[0560] In another embodiment, antibody and antibody compositions of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, heparin, warfarin, and aspirin. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and aspirin.

[0561] In another embodiment, antibody and antibody compositions of the invention are administered in combination with an agent that suppresses the production of anticardiolipin antibodies. In specific embodiments, the polynucleotides of the invention are administered in combination with an agent that blocks and/or reduces the ability of anticardiolipin antibodies to bind phospholipid-binding plasma protein beta 2-glycoprotein I (b2GPI).

[0562] In certain embodiments, antibody and antibody compositions of the invention are administered in combination with antiretroviral agents, nucleoside reverse

transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with antibody and antibody compositions of the invention to treat, prevent, and/or diagnose AIDS and/or to treat, prevent, and/or diagnose HIV infection.

[0563] In other embodiments, antibody and antibody compositions of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, antibody and antibody compositions of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, antibody and

antibody compositions of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat, prevent, and/or diagnose an opportunistic cytomegalovirus infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat, prevent, and/or diagnose an opportunistic fungal infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat, prevent, and/or diagnose an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat, prevent, and/or diagnose an opportunistic bacterial infection.

[0564] In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

[0565] In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, amoxicillin, aminoglycosides, beta-lactam (glycopeptide),

beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

[0566] Conventional nonspecific immunosuppressive agents, that may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs cyclophosphamide, cyclophosphamide IV, methylprednisolone, prednisolone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

[0567] In specific embodiments, antibody and antibody compositions of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucocorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[0568] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with steroid therapy. Steroids that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, oral corticosteroids, prednisone, and methylprednisolone (e.g., IV methylprednisolone). In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with prednisone. In a further specific embodiment, the antibody and antibody compositions of the invention are administered in combination with prednisone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and prednisone are those described herein, and include, but are not limited to, azathioprine, cylophosphamide, and cyclophosphamide IV. In a another specific embodiment, antibody and antibody compositions of the invention are administered in combination with methylprednisolone. In a further specific embodiment, the antibody and antibody compositions of the

invention are administered in combination with methylprednisolone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and methylprednisolone are those described herein, and include, but are not limited to, azathioprine, cyclophosphamide, and cyclophosphamide IV.

[0569] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial. Antimalarials that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, hydroxychloroquine, chloroquine, and/or quinacrine.

[0570] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an NSAID.

[0571] In a nonexclusive embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five, ten, or more of the following drugs: NRD-101 (Hoechst Marion Roussel), diclofenac (Dimethaid), oxaprozin potassium (Monsanto), mecaseprin (Chiron), T-614 (Toyama), pemetrexed disodium (Eli Lilly), atreleuton (Abbott), valdecoxib (Monsanto), eltenac (Byk Gulden), campath, AGM-1470 (Takeda), CDP-571 (Celltech Chiroscience), CM-101 (CarboMed), ML-3000 (Merckle), CB-2431 (KS Biomedix), CBF-BS2 (KS Biomedix), IL-1Ra gene therapy (Valentis), JTE-522 (Japan Tobacco), paclitaxel (Angiotech), DW-166HC (Dong Wha), darbufelone mesylate (Warner-Lambert), soluble TNF receptor 1 (synergen; Amgen), IPR-6001 (Institute for Pharmaceutical Research), trocade (Hoffman-La Roche), EF-5 (Scotia Pharmaceuticals), BIIL-284 (Boehringer Ingelheim), BIIF-1149 (Boehringer Ingelheim), LeukoVax (Inflammatics), MK-663 (Merck), ST-1482 (Sigma-Tau), and butixocort propionate (WarnerLambert).

[0572] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five or more of the following drugs: methotrexate, sulfasalazine, sodium aurothiomalate, auranofin, cyclosporine, penicillamine, azathioprine, an antimalarial drug (e.g., as described herein), cyclophosphamide, chlorambucil, gold, ENBREL™ (Etanercept), anti-TNF antibody, LJP 394 (La Jolla Pharmaceutical Company, San Diego, California) and prednisolone.

[0573] In a more preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial, methotrexate, anti-

TNF antibody, ENBREL™ and/or suflasalazine. In one embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate and anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with suflasalazine. In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate, anti-TNF antibody, and suflasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination ENBREL™. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™ and methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™, methotrexate and suflasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™, methotrexate and suflasalazine. In other embodiments, one or more antimalarials is combined with one of the above-recited combinations. In a specific embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), ENBREL™, methotrexate and suflasalazine. In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), sulfasalazine, anti-TNF antibody, and methotrexate.

[0574] In an additional embodiment, antibody and antibody compositions of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the antibody and antibody compositions of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[0575] CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVREND™), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

[0576] In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

[0577] In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

[0578] In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin,

vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, antibody and antibody compositions of the invention are administered in combination with Rituximab. In a further embodiment, antibody and antibody compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of the components of CHOP.

[0579] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with cytokines. Cytokines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, GM-CSF, G-CSF, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-alpha, IFN-beta, IFN-gamma, TNF-alpha, and TNF-beta. In preferred embodiments, antibody and antibody compositions of the invention are administered with BLySB Lymphocyte Stimulator (e.g., amino acids 134-285 of SEQ ID NO:3228). In another embodiment, antibody and antibody compositions of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, and IL-22. In preferred embodiments, the antibody and antibody compositions of the invention are administered in combination with IL4 and IL10.

[0580] In one embodiment, the antibody and antibody compositions of the invention are administered in combination with one or more chemokines. In specific embodiments, the antibody and antibody compositions of the invention are administered in combination with an α (CxC) chemokine selected from the group consisting of gamma-interferon inducible protein-10 (γ IP-10), interleukin-8 (IL-8), platelet factor-4 (PF4), neutrophil activating protein (NAP-2), GRO- α , GRO- β , GRO- γ , neutrophil-activating peptide (ENA-78), granulocyte chemoattractant protein-2 (GCP-2), and stromal cell-derived factor-1 (SDF-1, or pre-B cell stimulatory factor (PBSF)); and/or a β (CC) chemokine selected from the group consisting of: RANTES (regulated on activation, normal T expressed and secreted), macrophage inflammatory protein-1 alpha (MIP-1 α), macrophage inflammatory protein-1 beta (MIP-1 β), monocyte chemotactic protein-1 (MCP-1), monocyte chemotactic protein-2 (MCP-2), monocyte chemotactic protein-3 (MCP-3), monocyte chemotactic protein-4 (MCP-4) macrophage inflammatory protein-1 gamma (MIP-1 γ), macrophage inflammatory protein-3 alpha (MIP-3 α), macrophage

inflammatory protein-3 beta (MIP-3 β), macrophage inflammatory protein-4 (MIP-4/DC-CK-1/PARC), eotaxin, Exodus, and I-309; and/or the γ (C) chemokine, lymphotactin.

[0581] In another embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8, chemokine beta-1, and/or macrophage inflammatory protein-4. In a preferred embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8.

[0582] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with an IL-4 antagonist. IL-4 antagonists that may be administered with the antibody and antibody compositions of the invention include, but are not limited to: soluble IL-4 receptor polypeptides, multimeric forms of soluble IL-4 receptor polypeptides; anti-IL-4 receptor antibodies that bind the IL-4 receptor without transducing the biological signal elicited by IL-4, anti-IL4 antibodies that block binding of IL-4 to one or more IL-4 receptors, and muteins of IL-4 that bind IL-4 receptors but do not transduce the biological signal elicited by IL-4. Preferably, the antibodies employed according to this method are monoclonal antibodies (including antibody fragments, such as, for example, those described herein).

[0583] The invention also encompasses combining the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) with other proposed or conventional hematopoietic therapies. Thus, for example, the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) can be combined with compounds that singly exhibit erythropoietic stimulatory effects, such as erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, and triiodothyronine. Also encompassed are combinations of the antibody and antibody compositions of the invention with compounds generally used to treat aplastic anemia, such as, for example, methenolene, stanozolol, and nandrolone; to treat iron-deficiency anemia, such as, for example, iron preparations; to treat malignant anemia, such as, for example, vitamin B₁₂ and/or folic acid; and to treat hemolytic anemia, such as, for example, adrenocortical steroids, e.g., corticoids. See e.g., Resegotti et al., *Panminerva Medica*, 23:243-248 (1981); Kurtz, *FEBS Letters*, 14a:105-108 (1982); McGonigle et al., *Kidney Int.*, 25:437-444 (1984); and Pavlovic-Kantera, *Expt. Hematol.*, 8(supp. 8) 283-291 (1980), the contents of each of which are hereby incorporated by reference in their entireties.

[0584] Compounds that enhance the effects of or synergize with erythropoietin are also useful as adjuvants herein, and include but are not limited to, adrenergic agonists, thyroid hormones, androgens, hepatic erythropoietic factors, erythrotropins, and erythroginins, See for e.g., Dunn, "Current Concepts in Erythropoiesis", John Wiley and Sons (Chichester, England, 1983); Kalmani, *Kidney Int.*, 22:383-391 (1982); Shahidi, *New Eng. J. Med.*, 289:72-80 (1973); Urabe et al., *J. Exp. Med.*, 149:1314-1325 (1979); Billat et al., *Expt. Hematol.*, 10:133-140 (1982); Naughton et al., *Acta Haemat.*, 69:171-179 (1983); Cognote et al. in abstract 364, *Proceedings 7th Intl. Cong. of Endocrinology* (Quebec City, Quebec, July 1-7, 1984); and Rothman et al., 1982, *J. Surg. Oncol.*, 20:105-108 (1982). Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e., an amount which effects the formation of blood cells) of a pharmaceutical composition containing polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) to a patient. The polynucleotides and/or polypeptides of the invention and/or agonists or antagonists thereof is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further discussed herein. The pharmaceutical composition optionally contains one or more members of the group consisting of erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, triiodothyronine, methenolene, stanozolol, and nandrolone, iron preparations, vitamin B₁₂, folic acid and/or adrenocortical steroids.

[0585] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

[0586] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with fibroblast growth factors. Fibroblast growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[0587] Additionally, the antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic regimens, including but not limited to, radiation therapy. Such combinatorial therapy may be administered sequentially and/or concomitantly.

Kits

[0588] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[0589] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In an alternative embodiment, a kit comprises an antibody fragment that immunospecifically binds to BLySB Lymphocyte Stimulator. In a specific embodiment, the kits of the present invention contain a substantially isolated BLySB Lymphocyte Stimulator polypeptide as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with BLySB Lymphocyte Stimulator. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to BLySB Lymphocyte Stimulator (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized BLySB Lymphocyte Stimulator. The BLySB Lymphocyte Stimulator provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above-described kit includes a solid support to which BLySB Lymphocyte Stimulator is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to BLySB Lymphocyte Stimulator can be detected by binding of the said reporter-labeled antibody.

[0590] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with BLySB Lymphocyte Stimulator, and means for detecting the binding of BLySB Lymphocyte Stimulator to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0591] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound BLySB Lymphocyte Stimulator obtained by the methods of the present invention. After BLySB Lymphocyte Stimulator binds to a specific antibody, the unbound serum components are removed by washing, reporter-labeled anti-human antibody is added, unbound anti-human antibody is removed by washing, and a reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-BLySB Lymphocyte Stimulator antibody on the solid support. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate.

[0592] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0593] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant BLySB Lymphocyte Stimulator, and a reporter-labeled anti-human antibody for detecting surface-bound anti-BLySB Lymphocyte Stimulator antibody.

[0594] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0595] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

[0596] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880.

[0597] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128.

[0598] In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 1562.

[0599] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator.

[0600] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

[0601] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, and in which said antibody or fragment thereof immunospecifically binds to the membrane-bound form of BLySB Lymphocyte Stimulator.

[0602] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, and in which said antibody or fragment thereof immunospecifically binds to the soluble form of BLySB Lymphocyte Stimulator.

[0603] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator.

[0604] In specific embodiments, the present invention encompasses an antibody or

fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

[0605] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, and in which said antibody or fragment thereof immunospecifically binds to the membrane-bound form of BLySB Lymphocyte Stimulator.

[0606] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, and in which said antibody or fragment thereof immunospecifically binds to the soluble form of BLySB Lymphocyte Stimulator.

[0607] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0608] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, and in which said VL and said VH domains are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0609] In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator.

[0610] In specific embodiments, the antibody or fragment thereof of the invention is a whole immunoglobulin molecule.

[0611] In specific embodiments, the antibody or fragment thereof of the invention is a Fab fragment.

[0612] In specific embodiments, the antibody or fragment thereof of the invention

is a Fv fragment.

[0613] In specific embodiments, the present invention encompasses a chimeric protein comprising the antibody or fragment thereof of the invention covalently linked to a heterologous polypeptide.

[0614] In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLySB Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0615] In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLySB Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0616] In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLySB Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and wherein each type of antibody or fragment thereof further comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0617] In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLySB Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 3129 to 3227.

[0618] In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLySB Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128.

[0619] In specific embodiments, the present invention encompasses a panel of two

or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLySB Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128.

[0620] In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLySB Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128 and wherein each type of antibody or fragment further comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0621] In specific embodiments, the present invention encompasses a panel of two or more antibodies or fragments or variants thereof, each of which type immunospecifically binds to BLySB Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VHCDR3 from a different scFv having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

[0622] In specific embodiments, the antibodies or fragments thereof of the antibody panel of the invention, are each in a well of a 96 well plate.

[0623] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator.

[0624] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator.

[0625] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of

SEQ ID NOS: 1881 to 1908, wherein the antibody of fragment thereof immunospecifically binds the membrane-bound form of BLySB Lymphocyte Stimulator.

[0626] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1569, wherein said antibody of fragment thereof immunospecifically binds the soluble form of BLySB Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0627] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0628] In specific embodiments, the present invention encompasses an isolated

nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0629] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, wherein the antibody or fragment thereof immunospecifically binds the membrane-bound form of BLySB Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0630] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of

SEQ ID NOS: 1563 to 1880, wherein said antibody or fragment thereof immunospecifically binds the soluble form of BLySB Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0631] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0632] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically

binds BLySB Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and in which said VL domain and said VH domain are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0633] In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VHCDR3 from an scFv having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

[0634] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of

SEQ ID NOS: 1 to 2128.

[0635] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0636] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0637] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0638] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0639] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

[0640] In specific embodiments, the present invention provides an antibody or

fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH CDR3 encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

[0641] In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH CDR3 encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

[0642] In specific embodiments, the present invention provides a method for detecting of aberrant expression of BLySB Lymphocyte Stimulator, comprising:

[0643] assaying the level of BLySB Lymphocyte Stimulator expression in cells or a tissue sample of an individual using one or more antibodies or fragments or variants thereof that immunospecifically bind BLySB Lymphocyte Stimulator; and

[0644] comparing the level of BLySB Lymphocyte Stimulator assayed in the cells or a tissue sample with a standard level of BLySB Lymphocyte Stimulator or a level of BLySB Lymphocyte Stimulator in cells or a tissue sample from an individual without aberrant BLySB Lymphocyte Stimulator expression, wherein an increase or decrease in the assayed level of BLySB Lymphocyte Stimulator or level in cells or a tissue sample from an individual without aberrant BLySB Lymphocyte Stimulator expression compared to the standard level of BLySB Lymphocyte Stimulator is indicative of aberrant expression.

[0645] In specific embodiments, the present invention provides a method for diagnosing a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression or activity, comprising:

[0646] administering to a subject an effective amount of a labeled antibody or fragment thereof that immunospecifically binds to BLySB Lymphocyte Stimulator;

[0647] waiting for a time interval following the administering for permitting the labeled antibody or fragment thereof to preferentially concentrate at sites in the subject where BLySB Lymphocyte Stimulator is expressed;

- [0648] determining background level; and
- [0649] detecting the labeled antibody or fragment thereof in the subject, such that detection of labeled antibody or fragment thereof above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of BLySB Lymphocyte Stimulator.
- [0650] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.
- [0651] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.
- [0652] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.
- [0653] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent.
- [0654] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase.
- [0655] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin.
- [0656] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is ^{125}I , ^{131}I , ^{111}In , ^{90}Y or ^{99}Tc .
- [0657] In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is luciferase, luciferin or aequorin.
- [0658] A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VH domain from an scFv having an amino acid

sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

[0659] A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

[0660] A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier.

[0661] A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

[0662] A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

[0663] A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition

comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

[0664] A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

[0665] A method of treating, preventing or ameliorating a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition of comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds BLySB Lymphocyte Stimulator and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

[0666] This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

EXAMPLES

Abbreviations

0.2 M Tris-HCl, 0.5 mM EDTA, 0.5 M sucrose (TES)
1-ethyl-3-[3-dimethylaminopropyl]carbo diimide hydrochloride (EDC)
2TY supplemented with 100µg/ml ampicillin and 2% glucose (2TYAG)
2TY supplemented with 100µg/ml ampicillin and 50µg/ml kanamycin (2TYAK)
3,3',5,5'-Tetramethyl Benzidine (TMB)
50% inhibitory concentration (IC₅₀)
6xPBS containing 18% Marvel blocking solution (6xMPBS)
Absorbance (A)
Bovine serum albumin (BSA)
Enzyme linked immunosorbent assay (ELISA)
Foetal calf serum (FCS)
Heavy chain variable (V_H)
Hepes buffered saline (HBS)
Horseradish peroxidase (HRP)
Immobilised Metal Affinity Chromatography (IMAC)
Isopropyl β-D-thiogalactopyranoside (IPTG)
Light chain variable(V_L)
Multiplicity of infection (MOI)
N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid] (Hepes)
Nanomolar (nM)
N-Hydroxysuccinimide (NHS)
PBS containing 3% Marvel (MPBS)
Phosphate Buffered Saline (PBS)
Phosphate Buffered Saline + 0.1% (v/v) Tween 20 (PBST)
Picomolar (pM)
Single chain fragment variable (scFv)
Tumour Necrosis Factor-alpha (TNF-α)
Tumour Necrosis Factor-beta (TNF-β)
TNF-related apoptosis inducing ligand (TRAIL)

Definitions:

[0667] In the following section “immobilized BLySB Lymphocyte Stimulator” refers to a soluble form of BLySB Lymphocyte Stimulator or biotinylated BLySB Lymphocyte Stimulator coated on a plastic assay plate (e.g., a 96 well plate), but does not refer to histidine tagged BLySB Lymphocyte Stimulator coated on a plastic assay plate.; “biotinylated BLySB Lymphocyte Stimulator” is a soluble form of BLySB Lymphocyte Stimulator except when used to coat an ELISA plate, in which case it would be “immobilized BLySB Lymphocyte Stimulator.” Membrane bound forms of BLySB Lymphocyte Stimulator include, but are not limited to, U937 and P388 plasma membranes.

Example 1: Antibodies Immunospecifically Binding to Soluble And Membrane-Bound BLySB Lymphocyte Stimulator

[0668] A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator. Phage displaying scFvs that bound to immobilized BLySB Lymphocyte Stimulator were identified after panning on immobilized BLySB Lymphocyte Stimulator and assessment by ELISA for binding to immobilized BLySB Lymphocyte Stimulator. The BLySB Lymphocyte Stimulator that was immobilized on plates for these assays was purified from supernatants of Sf9 cells infected with a baculovirus expression construct as described in Moore et al., Science 285:260-263 which is hereby incorporated by reference in its entirety. Each of the identified scFvs were then sequenced. Certain sequences were isolated multiple times, thus a panel (panel 1) containing one member of each unique sequences was generated and further characterized for their ability to immunospecifically bind to the soluble and membrane-bound forms of BLySB Lymphocyte Stimulator.

[0669] The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual V_H and V_L segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, www.mre-cpe.cam.ac.uk which can accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

Example 2: Specificity of scFvs for BLySB Lymphocyte Stimulator and Membrane-Bound BLySB Lymphocyte Stimulator

[0670] The specificity of each of the scFvs for both BLySB Lymphocyte Stimulator and membrane-bound BLySB Lymphocyte Stimulator was determined by phage ELISA. BLySB Lymphocyte Stimulator was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937.

Maintenance of U937 Cells

[0671] U937 cells are a human monocyte-like, histiocytic lymphoma cell line known to express BLySB Lymphocyte Stimulator on their plasma membranes. They were maintained in RPMI-1640 supplemented with 4mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells were thawed from frozen stock and are either used for plasma membrane preparation, or split 1:5, after 2 days in culture when the cell density reaches $1 \times 10^6/\text{ml}$.

Preparation of U937 Plasma Membranes

[0672] To prepare plasma membranes, 1×10^9 U937 cells were harvested from their culture medium by centrifugation at 1000 rpm at 4°C for 5 minutes in a benchtop centrifuge. The cells were resuspended in 40 ml 12 mM Tris, pH 7.5, 250 mM sucrose and placed on ice. The cells are then lysed using a hand-held electric homogenizer (Labortechnik IKA Ultra-Turrax) for four, one minute, bursts. To check that cell lysis had occurred, 10 µl cell lysate was added to 10 µl Trypan blue and the cell lysate was examined under a microscope. After confirming lysis, the homogenate was centrifuged at 270 x g, for 10 minutes at 4°C to pellet the nuclear fraction and the supernatant was retained. The supernatant was centrifuged at 8000 x g, 10 mins, 4°C, to pellet the mitochondrial and lysosomal fractions and the supernatant was retained. The supernatant was then centrifuged at 100000 x g, 60 mins, 4°C to pellet the plasma membrane enriched fraction. The supernatant was discarded and the plasma membrane pellet was resuspended in 1 ml PBS and stored at -70°C. The protein concentration of the plasma membrane fraction was determined using a protein quantification kit (Biorad). Typical yields were between 5 and 10 mg of plasma membranes.

Phage ELISA

[0673] To determine the specificity of each of the unique scFvs, a phage ELISA was performed for each scFv against human BLySB Lymphocyte Stimulator, U937 plasma membranes, TNF α (R&D Systems, Minneapolis, MN), BSA and uncoated well. Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100 μ l 2TYAG medium per well. Plates were incubated at 37°C for 4 hours, shaking. M13KO7 helper phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37°C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 μ l 2TYAK and incubated at 30°C overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100 μ l phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Twenty μ l of 6xMPBS was added to each well, and incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

[0674] Flexible 96-well plates (Falcon) were coated overnight at 4°C with human BLySB Lymphocyte Stimulator (1 μ g/ml) in PBS, U937 plasma membranes (10 μ g/ml) in PBS, TNF α (1 μ g/ml) in PBS, BSA (1 μ g/ml) in PBS, or PBS. After coating, the solutions were removed from the wells, and the plates were blocked for 1 hour at room temperature in MPBS. The plates were washed 3 times with PBS and then 50 μ l of pre-blocked phage was added to each well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50 μ l of an anti-gene VIII-HRP conjugate (Pharmacia) at a 1 to 5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50 μ l of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1/50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty μ l of TMB substrate was then added to each well, and incubated at room temperature for 30 minutes or until colour development. The reaction was stopped by the addition of 25 μ l of 0.5 M H₂SO₄. The signal generated was measured by reading the absorbance at 450nm (A₄₅₀) using a microtiter plate reader (Bio-Rad 3550).

[0675] The results for 3 clones (I006E07, I008D05 and I016F04) are shown in Figure 1. All 3 scFvs recognize immobilized BLySB Lymphocyte Stimulator and U937 plasma membranes but do not recognize TNF α , BSA or an uncoated well (PBS only). These results indicate that these scFvs specifically recognize immobilized BLySB Lymphocyte Stimulator and membrane-bound BLySB Lymphocyte Stimulator.

Example 3: Inhibition in an *In Vitro* Receptor Binding Assay by Phage ScFvs

[0676] All of the unique phage scFvs in panel 1 were assessed for their ability to inhibit soluble BLySB Lymphocyte Stimulator binding to its cognate receptor on IM9 cells.

Biotinylation of BLySB Lymphocyte Stimulator

[0677] One hundred μ g of either human or mouse BLySB Lymphocyte Stimulator was dialysed overnight at 4° C against 50 mM sodium bicarbonate (sodium hydrogen carbonate) pH8.5 using a slide-a-lyzer cassette (Pierce). The next day, NHS-biotin (Pierce) was dissolved in DMSO to 13.3 mg/ml. This was then added to the BLySB Lymphocyte Stimulator at a molar ratio of 20:1 biotin:BLySB Lymphocyte Stimulator, mixed and incubated on ice for 2 hours. The biotinylated BLySB Lymphocyte Stimulator was then dialysed back into sterile PBS (Sigma) using a slide-a-lyzer cassette overnight at 4°C. The biological activity of the biotinylated BLySB Lymphocyte Stimulator was confirmed using the receptor binding inhibition assay (see below).

Maintenance of IM9 cells

[0678] IM9 cells are a human B lymphocyte cell line. They were maintained in RPMI-1640 supplemented with 4 mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells are thawed from frozen stock and can be used in assays after 5 days in culture when they reach a density of 4 - 8 x 10⁵ /ml.

Receptor binding inhibition assay

[0679] Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100 μ l 2TYAG medium per well. Plates were incubated at 37° C for 4 hours, shaking. M13KO7 helper

phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37°C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 µl 2TYAK and incubated at 30°C overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100 µl phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Phage were diluted 1 in 2 in MPBS prior to use.

[0680] Flat-bottomed 96-well plates (Costar) were coated with 100 µl per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4°C overnight. One hundred µl of IM9 cells (at 10⁶/ml in RPMI-1640 culture medium) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was carefully aspirated and 200 µl of MPBS added to each well. The plates were then allowed to block for 1 hour at room temperature.

[0681] To a separate 96-well plate 10 µl of biotinylated BLySB Lymphocyte Stimulator (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Fifty-five µl of each appropriate phage supernatant was added to each well and the final volume in each well was 65 µl. Plates were then incubated at room temperature for 30 minutes.

[0682] The IM9 coated plates were washed twice in PBS, tapped dry and immediately 50 µl of the phage/biotinylated-BLySB Lymphocyte Stimulator mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50 µl of streptavidin-Delfia (Wallac) was added to each well at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100 µl per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nM.

[0683] Results for 3 phage scFvs (I001C09, I018D07 and I016H07) that inhibited the binding of biotinylated BLySB Lymphocyte Stimulator are shown in Figure 2. Maximal binding of biotinylated BLySB Lymphocyte Stimulator to its receptor (bio-

BLySB Lymphocyte Stimulator only), the background signal in the absence of biotinylated BLySB Lymphocyte Stimulator (no bio-BLySB Lymphocyte Stimulator), and results with an irrelevant (*i.e.*, does not recognize BLySB Lymphocyte Stimulator) phage antibody are also shown. All 3 phage scFvs inhibited biotinylated BLySB Lymphocyte Stimulator binding to its receptor on IM9 cells, identifying these scFvs as scFvs that bind the soluble form of BLySB Lymphocyte Stimulator. These scFvs also bind to U937 membranes, thus they also bind the membrane bound form of BLySB Lymphocyte Stimulator.

[0684] Forty-eight of the scFvs from panel 1 that demonstrated the greatest inhibition as phage particles in this assay were chosen for further study. These 48 scFvs are listed in Table 3.

Table 3. scFvs that Inhibit the Binding of Biotinylated-BLySB Lymphocyte Stimulator to its Receptor

Antibody	Antibody	Antibody	Antibody	Antibody
I008C02	I029D07	I008C03	I008C12	I028A06
I022E02	I061E07	I007H08	I061H01	I031C03
I018C02	I006D07	I008A11	I006D08	I031F02
I008B01	I017D10	I061D02	I026E03	I031F09
I016F04	I007B03	I008A09	I027A07	I031G11
I016E05	I018C10	I007F11	I016H07	I050A07
I018H08	I001C09	I037E07	I021B05	I050A12
I018H09	I018D07	I037E12	I031G10	I050B11
	I029F11	I016F02	I031G08	I051C04
	I022D01		I031C07	I003F12
			I012A06	

Example 4: Specificity of Anti-BLySB Lymphocyte Stimulator Antibodies

[0685] The specificity of the 48 scFvs listed in Table 3 for human and murine BLySB Lymphocyte Stimulator was determined using phage ELISA.

Phage ELISA

[0686] To determine the specificity of the 48 scFvs, a phage ELISA was performed against human and mouse BLySB Lymphocyte Stimulator, and a panel of related and unrelated human antigens: Fas ligand, TRAIL, TNF α , TNF β , and PBS. The : Fas ligand, TRAIL, TNF α , and TNF β antigens were obtained from R&D Systems, Minneapolis, MN. Individual *E. coli* colonies containing phagemid were inoculated into 5 ml 2YTAG and incubated at 37°C for 4 hours, shaking. M13KO7 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37°C for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30°C overnight with shaking. The next day, the cells were pelleted by centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatant (5 ml) was carefully transferred to a fresh tube, 1 ml of 6MPBS was added, and the tube was incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

[0687] All antigens were coated at 1 μ g/ml. ELISAs were performed essentially as described in Example 2. The only exception to this being the detection of phage antibody binding to mouse BLySB Lymphocyte Stimulator where the step involving incubation with the HRP-labelled anti-mouse polymer was omitted. Binding to mouse BLySB Lymphocyte Stimulator was detected with TMB as in Section Example 2.

[0688] All 48 scFvs are specific for immobilized human BLySB Lymphocyte Stimulator and 43 out of the 48 scFvs cross-react with immobilized mouse BLySB Lymphocyte Stimulator but not with any other unrelated or related antigen tested. I008C03, I007F11, I037E07, I037E12, and I016H07 did not bind murine BLySB Lymphocyte Stimulator. Results for two scFvs, I022D01 and I031F02, are shown in Figure 3. Both these scFvs specifically recognize human and mouse BLySB Lymphocyte Stimulator but not any other unrelated or related antigen tested.

Example 5: Specificity for the Membrane-Bound Form of BLySB Lymphocyte Stimulator

[0689] The specificity of 48 scFvs for membrane-bound BLySB Lymphocyte Stimulator was determined by the phage ELISA described in Example 2. BLySB Lymphocyte Stimulator was immobilised onto plastic as a membrane-bound form present on plasma membranes preparations from the human macrophage-like cell line, U937. This cell line is known to express the membrane-bound form of human BLySB Lymphocyte Stimulator.

[0690] To demonstrate that this binding is specific for membrane-bound BLySB Lymphocyte Stimulator, a competition ELISA was developed to determine if the ELISA signal for an individual antibody on U937's could be competed out by pre-incubation with either BLySB Lymphocyte Stimulator or TNF α . An anti-BLySB Lymphocyte Stimulator antibody that also recognizes membrane-bound BLySB Lymphocyte Stimulator would be expected to demonstrate a signal reduction with free BLySB Lymphocyte Stimulator but not free TNF α .

Competition ELISA

[0691] Individual *E. coli* colonies containing phagemid for each of the 48 scFvs listed in Table 3 were inoculated into 5 ml 2YTAG and incubated at 37°C for 4 hours, shaking. M13KO7 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37° C for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30°C overnight with shaking. The next day, the cells were pelleted by centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatants (5 ml) were carefully transferred to a fresh tube.

[0692] For each of the 48 scFvs listed in Table 3, two aliquots of 20 μ l 6xMPBS were pipetted into separate wells of a 96-well plate (Greiner). The first aliquot was supplemented with BLySB Lymphocyte Stimulator to a final concentration of 0.5 μ g/ml. The second aliquot was supplemented with TNF- α to a final concentration of 0.5 μ g/ml. Each experiment was performed in triplicate. One hundred μ l of each phage supernatant was then added to each aliquot and mixed by pipetting up and down. The phage were incubated (\pm competing antigen) at room temperature for 1 hour.

[0693] Flexible 96-well plates (Falcon) were coated overnight at 4°C with 50 µl of 10 µg/ml U937 plasma membranes. After coating, the plates were washed 3 times with PBS and blocked for 1 hour at room temperature with 200 µl MPBS. The plates were washed 3 times with PBS and 50 µl of phage (\pm competing antigen) was added to each appropriate well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50 µl of a mouse anti-gene VIII-HRP conjugate (Pharmacia) at a 1:5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50 µl of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1:50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty µl of TMB substrate was then added to each well, and incubated at room temperature for 30 to 60 minutes or until color development. The reaction was stopped by the addition of 25 µl of 0.5 M H₂SO₄. The signal generated was measured by reading the absorbance at 450nm (A₄₅₀) using a microtiter plate reader (Bio-Rad 3550).

[0694] All 48 scFvs bind to U937 plasma membrane preparations. This signal could be competed out by pre-incubation of the phage antibody with BLySB Lymphocyte Stimulator but not by pre-incubation with TNF- α . This indicates that the 48 scFvs specifically recognize membrane-bound BLySB Lymphocyte Stimulator as well as soluble BLySB Lymphocyte Stimulator. Typical results are exemplified by scFvs I031F09, I050A12 and I051C04 and are shown in Figure 4. All 3 scFvs demonstrate binding to U937 plasma membranes. This binding was specifically competed out with BLySB Lymphocyte Stimulator but did not compete with TNF- α , demonstrating specific recognition of membrane-bound BLySB Lymphocyte Stimulator.

Example 6: scFv Off-rate Determinations

[0695] All off-rate determinations were performed on BIAcore 2000 machines, using the BIAcore 2000 Control Software and evaluated using the BIAevaluation 3.0 software.

Preparation of a Low Density BLySB Lymphocyte Stimulator Surface

[0696] A 500RU surface was prepared for kinetic studies with purified scFvs. A low density BLySB Lymphocyte Stimulator surface (500 RU BLySB Lymphocyte Stimulator coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram initiated with HBS buffer at a flow rate of 5 µl/min. The NHS and EDC coupling solutions (BIAcore) were mixed according to manufacturer's instructions and 30 µl injected over the CM5 surface. Fifty µl of BLySB Lymphocyte Stimulator at 1 µg/ml in 10 mM sodium acetate buffer, pH4, was then injected followed by 30 µl of ethanolamine-HCl solution (BIAcore). The flow rate was then adjusted to 20 µl/min and 10 µl of 4M guanidine hydrochloride in HBS injected over the surface. This strips the surface of non-covalently bound BLySB Lymphocyte Stimulator.

Measurement of scFv off-rate kinetics on the low density surfaces

[0697] The chip containing the low density BLySB Lymphocyte Stimulator surface was inserted in to the BIAcore. A dilution series of purified scFvs was prepared in HBS, typically 50 µg/ml doubling dilutions down to 1.5 ug/ml. The dilution series was then injected sequentially over the low density BLySB Lymphocyte Stimulator surface (and blank control) using the following program:

MAIN

FLOWCELL 1,2,3,4

APROG	genab	r1d1	ab1
APROG	genab	r1d2	ab2
APROG	genab	r1d3	ab3
APROG	genab	r1d4	ab4
APROG	genab	r1d5	ab5
APROG	genab	r1d6	ab6

APPEND CONTINUE

END

DEFINE APROG genab

```

PARAM %Abpos %AbId
FLOW      20
KINJECT   %Abpos 200 80
INJECT    r1c6 10!guanidine hydrochloride regeneration step
EXTRACLEAN
END

```

[0698] Bound scFvs were removed by injecting 10µl 4M GuHCl in HBS over the surface between scFv samples.

[0699] The binding curves for individual scFvs were analyzed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, I003C02, is shown in Figure 5. I003C02 has a $K_{\text{off}} = 6 \times 10^{-3} \text{ s}^{-1}$.

Example 7: Inhibition in an *In Vitro* Receptor Binding Assay by scFv Antibodies

[0700] The 48 scFvs listed in Table 3 were purified and assessed for their ability to inhibit BLySB Lymphocyte Stimulator binding to its receptor on IM9 cells.

Purification of scFv

[0701] To determine the inhibitory potency of anti-BLySB Lymphocyte Stimulator scFv, scFv's were first prepared by IMAC. 2TYAG (5 ml) was inoculated with a single colony and grown overnight at 30°C, shaking. This overnight culture was then used to inoculate 500 ml of 2TY containing 100 µg/ml ampicillin and 0.1% Glucose, and grown at 30° C, shaking, until an A_{600} of 1.0 was attained. IPTG was added to 1 mM and the culture was grown for a further 3.5 hours at 30°C.

[0702] Cells were harvested by centrifugation at 5,000rpm, and resuspended in 10 ml of TES. A further 15 ml of a 1:5 dilution (in water) of TES was added, and the cell suspension incubated on a turning wheel at 4°C for 30 minutes. This causes osmotic shock and yields a periplasmic extract containing the scFv. Residual cells and debris were pelleted by centrifugation at 9,000 rpm for 20 minutes at 4°C. The supernatant was transferred to a new tube, and 50 µl of 1 M MgCl_2 added. Two ml of a Ni-NTA agarose (Qiagen), pre-washed with buffer (50 mM sodium phosphate, pH 8, 300 mM NaCl) together with a protease inhibitor tablet (Boehringer Mannheim) were then added to the

periplasmic extract. The preparation was incubated, rotating, overnight at 4°C. The Ni-NTA was pelleted by centrifugation at 2,000 rpm for 5 minutes, and the supernatant was aspirated. The agarose beads were washed 3 times with 50 ml wash buffer, centrifuging to collect the agarose in between each wash. Ten ml of wash buffer was added after the final wash, and the slurry was loaded on to a polyprep column (BioRad). Two ml elution buffer (50 mM NaPi (sodium phosphate), pH 8, 300 mM NaCl, 250 mM imidazole) was added to the drained agarose, and the eluate was collected. IMAC purified scFv was buffer exchanged in to PBS by use of a Nap 5 column (Pharmacia) according to the manufacturer's instructions. The A₂₈₀ was read and the protein concentration determined using a molar extinction coefficient of 1 mg/ml protein = A₂₈₀ 1.4. Purified scFv was stored in 500 µl aliquots at -70°C.

Receptor Binding Inhibition Assay

[0703] Flat-bottomed 96-well plates (Costar) were coated with 100 µl per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4 °C overnight. One hundred µl of IM9 cells (at 10⁶/ml in RPMI-1640) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was carefully aspirated and 200 µl of MPBS added to each well. The plates were then left to block for 1 hour at room temperature.

[0704] To a separate 96-well plate, titrate test scFvs in MPBS, in triplicate, over a concentration range from 10 µg/ml down to 0.001 µg/ml were added. The final volume of test scFv in each well was 55 µl. Competition with unlabelled BLySB Lymphocyte Stimulator was also included in every assay as a control. Unlabelled BLySB Lymphocyte Stimulator, in MPBS, was typically titrated in triplicate, over a concentration range from 1 µg/ml down to 0.001 µg/ml. 10 µl of biotinylated-BLySB Lymphocyte Stimulator (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Plates were then incubated at room temperature for 30 minutes.

[0705] The IM9 coated plates was washed twice in PBS, tapped dry and immediately 50µl of the scFv/biotinylated-BLySB Lymphocyte Stimulator mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50 µl per well added of streptavidin-Delfia

(Wallac) at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100µl per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nM.

[0706] Typical titration curves for two scFv antibodies, I007F11 and I050A07, are shown in Figure 6. Unlabelled BLySB Lymphocyte Stimulator competed for binding to its receptor with an IC₅₀ value of 0.8 nM. The IC₅₀ values for I007F11 and I050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown. The 9 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 4. This data also confirms that these 9 scFvs recognize the soluble form of BLySB Lymphocyte Stimulator.

Table 4: 9 ScFvs that demonstrated greatest potency in BLySB Lymphocyte Stimulator Receptor Binding Inhibition Assay

ScFv Antibody
I017D10
I022D01
I008A11
I006D08
I031F02
I050A12
I050B11
I051C04
I003F12S

Example 8: Antibodies recognizing a soluble form of BLySB Lymphocyte Stimulator

[0707] A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble but not the membrane-bound forms of BLySB Lymphocyte Stimulator.

[0708] A phage library was screened for the ability to bind to biotinylated BLySB Lymphocyte Stimulator. The phage were exposed to biotinylated BLySB Lymphocyte Stimulator, allowed an interval of time to bind the biotinylated BLySB Lymphocyte Stimulator. Phage binding bio-BLySB Lymphocyte Stimulator were then isolated by capture on streptavidin coated magnetic beads.

[0709] The phage identified in the screen above (capture of Bio-BLySB Lymphocyte Stimulator from solution) were then screened by ELISA for their ability to bind immobilized BLySB Lymphocyte Stimulator. The scFv expressed by phage that bound immobilized BLySB Lymphocyte Stimulator were then cloned and sequenced. Again, several sequences were identified multiple times, thus a panel (panel 2) consisting of an example of each phage expressing a unique scFv was then characterized further.

[0710] The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual V_H and V_L segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, www.mrc-cpe.cam.ac.uk which can be accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

Example 9: Specificity For Soluble BLySB Lymphocyte Stimulator

[0711] The scFvs were isolated from a library of phage based on their ability to bind a soluble form of BLySB Lymphocyte Stimulator. Briefly, phage were preincubated with biotinylated BLySB Lymphocyte Stimulator in solution. Phage that bound to this biotinylated BLySB Lymphocyte Stimulator were then isolated using streptavidin coated magnetic beads.

[0712] The specificity of each of the unique scFvs for BLySB Lymphocyte Stimulator and for the membrane-bound form of BLySB Lymphocyte Stimulator, was determined by phage ELISA. BLySB Lymphocyte Stimulator was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937. Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

Phage ELISA

[0713] To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against human BLySB Lymphocyte Stimulator, U937 plasma membranes, TNF α , BSA and an uncoated well. Antigen coating conditions were as described in Example 2, apart from human BLySB Lymphocyte Stimulator. BLySB Lymphocyte Stimulator was first biotinylated (as described in Example 3) and coated at 1 μ g/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

[0714] The results for 3 clones (I074B12, I075F12 and I075A02) that bind the soluble but not the membrane-bound form of BLySB Lymphocyte Stimulator are shown in Figure 7. As a control, a phage antibody that recognizes TNF α , is also shown in Figure 7. There is a small non-specific background signal on the U937 plasma membranes that is evident with both the anti-BLySB Lymphocyte Stimulator scFvs as well as the anti-TNF α control. All 3 anti-BLySB Lymphocyte Stimulator scFvs recognize BLySB Lymphocyte Stimulator but not U937 plasma membranes, TNF α , BSA or an uncoated well (PBS only). This indicates that the scFvs do not bind the membrane-bound form of BLySB Lymphocyte Stimulator. Further, The fact that these scFvs were isolated on the basis of their ability to bind soluble biotinylated BLySB Lymphocyte Stimulator indicates that they bind the soluble form of BLySB Lymphocyte Stimulator. Further confirmation of these scFvs' specificity for BLySB Lymphocyte Stimulator is provided in Example 10.

Example 10: Inhibition in an *in vitro* receptor binding assay by phage scFvs

[0715] All of the unique phage scFvs from panel 2 were assessed for their ability to inhibit BLySB Lymphocyte Stimulator binding to its cognate receptor on IM9 cells. The biotinylation of BLySB Lymphocyte Stimulator, maintenance of IM9 cells and receptor binding inhibition assay were performed as described in Example 3.

[0716] Results for two phage scFvs, I0025B09 and I026C04 are shown in Figure 8. Maximal binding of biotinylated BLySB Lymphocyte Stimulator to its receptor (bio-BLySB Lymphocyte Stimulator only), the background signal in the absence of biotinylated BLySB Lymphocyte Stimulator (no bio-BLySB Lymphocyte Stimulator), and results with an irrelevant (i.e. does not recognize BLySB Lymphocyte Stimulator) phage

antibody are also shown. Both phage scFvs inhibited biotinylated BLySB Lymphocyte Stimulator binding to its receptor on IM9 cells. 33 of the unique scFvs from panel 2 were identified for further study. These 33 scFvs demonstrated the greatest inhibition as phage particles in this assay and are listed in Table 5.

Table 5: Identification of 33 phage scFvs to free BLySB Lymphocyte Stimulator that demonstrate the most significant inhibition of biotinylated-BLySB Lymphocyte Stimulator binding to its receptor

Antibody	Antibody	Antibody	Antibody
I026C04	I074B12	I073F04	I065D04
I003C06	I075A02	I078D08	I068C08
I025B09	I068B08	I078D02	I068F03
I027B12	I068B04	I075G01	I069B07
I025B06	I068C06	I071B03	
I030A10	I075F12	I072B09	
I002A01R	I065D08	I078H08	
I002A01K	I065F08	I064C04	
I026C04R	I067B10	I064C07	
I026C04K	I067F05		

Example 11: Specificity of anti-BLySB Lymphocyte Stimulator scFvs

[0717] The specificity of the 33 scFvs (listed in Table 5) for immobilized human and murine BLySB Lymphocyte Stimulator was determined using phage ELISA.

Phage ELISA

[0718] To determine the specificity of the 33 scFvs, a phage ELISA was performed as described in Example 4 against human and mouse BLySB Lymphocyte Stimulator, and a panel of related human antigens: TRAIL, LIGHT, TNF α , TNF β , and an uncoated well (PBS only).

[0719] Typical results for two scFvs, I067F05 and I078D02 are shown in Figure 9. A control antibody that specifically recognizes TNF α is also shown. Both anti-BLySB Lymphocyte Stimulator scFvs specifically recognize immobilized human and mouse BLySB Lymphocyte Stimulator but not any other antigen tested.

[0720] All 33 scFvs are specific for human BLySB Lymphocyte Stimulator. 14/33 cross-react with mouse BLySB Lymphocyte Stimulator but not with any other unrelated or

related antigen tested.

Example 12: scFv Off-Rate Determinations

[0721] Off-rate determinations, preparation of a low density BLySB Lymphocyte Stimulator surface and kinetic measurements were as detailed in Example 6.

[0722] The binding curves for individual scFvs were analysed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, I002A01, is shown in Figure 10. I002A01 has a $K_{\text{off}} = 9 \times 10^{-4} \text{ s}^{-1}$.

Example 13: Inhibition in an *in vitro* receptor binding assay by scFv antibodies

[0723] The 33 scFvs identified in Table 5 were prepared as purified scFvs and assessed for their ability to inhibit BLySB Lymphocyte Stimulator binding to its receptor on IM9 cells. The scFvs were purified and analysed in the receptor binding inhibition assay as described in Example 6.1.8.

[0724] Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in Figure 11. Unlabelled BLySB Lymphocyte Stimulator competed for binding to its receptor with an inhibitory constant 50 (IC_{50}) value of 0.66 nM. The IC_{50} values for I0068C06 and I074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown. The 7 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 6.

Table 6: Identification of 7 scFvs to free BLySB Lymphocyte Stimulator that demonstrate the most significant inhibition of biotinylated-BLySB Lymphocyte Stimulator binding to its receptor as purified scFv's.

Antibody
I002A01-R
I002A01-K
I026C04-R
I026C04-K
I068C06
I075F12
I067B10

Example 14: ScFvs Recognizing Membrane-bound BLySB Lymphocyte Stimulator

[0725] A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the membrane-bound but not the soluble form of BLySB Lymphocyte Stimulator.

[0726] As a starting point, a library of phage expressing scFv antibodies were panned on immobilized HIS-tagged BLySB Lymphocyte Stimulator. Phage isolated by panning were then screened for the ability to bind to HIS-tagged BLySB Lymphocyte Stimulator. HIS-tagged BLySB Lymphocyte Stimulator was obtained by expressing amino acids 71-285 of SEQ ID NO:3228 using the pQE9 vector (Qiagen Inc., Valencia, CA) in *E. coli* and purifying the expressed protein. This phage clones identified by this screen were then sequenced. After sequencing, A panel (panel 3) of phage each expressing a unique scFv that bound HIS-tagged BLySB Lymphocyte Stimulator was generated and further characterized.

[0727] The derived amino acid sequences of the unique scFvs from panel 3 are shown in Table 1 above. The individual V_H and V_L segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, www.mre-epc.cam.ac.uk which can accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

Example 15: Recognition of Membrane-bound BLySB Lymphocyte Stimulator

[0728] The specificity of each of the unique scFvs for both the membrane-bound form of BLySB Lymphocyte Stimulator as well as for the soluble form of BLySB Lymphocyte Stimulator, was determined by phage ELISA.

[0729] BLySB Lymphocyte Stimulator was immobilised onto plastic either directly as a purified soluble form of the protein or biotinylated and coated on a streptavidin plate as in Example 9. Binding to HIS-tagged BLySB Lymphocyte Stimulator was used as a primary screen for scFv's that would bind the membrane-bound form of BLySB Lymphocyte Stimulator (see below). The membrane-bound form of BLySB Lymphocyte Stimulator was presented as plasma membranes preparations from the human macrophage-like cell line, U937 or the murine cell line P388.

[0730] Mouse monoclonal antibodies have been raised against His-tagged BLySB

Lymphocyte Stimulator according to standard procedures. Characterization of these mouse monoclonal antibodies revealed that they specifically recognized both His-tagged BLySB Lymphocyte Stimulator and the membrane-bound form of BLySB Lymphocyte Stimulator on U937 cells, but not soluble BLySB Lymphocyte Stimulator. Therefore, specific recognition of His-tagged BLySB Lymphocyte Stimulator was used as supporting evidence for the recognition of the membrane-bound form of BLySB Lymphocyte Stimulator by phage and scFv antibodies.

Phage ELISA

[0731] To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against His-tagged human BLySB Lymphocyte Stimulator, U937 plasma membranes, TNF α , BSA and an uncoated well. Antigen coating conditions were as described in 2. apart from human BLySB Lymphocyte Stimulator. BLySB Lymphocyte Stimulator was first biotinylated (as described in Example 3) and coated at 1 μ g/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

[0732] The results for 3 clones, I079C01, I081C10 and I082A02, and a control phage antibody that recognizes TNF α , are shown in Figure 12. All 3 scFvs recognize U937 plasma membranes (U937) and His-tagged BLySB Lymphocyte Stimulator (HIS-BLySB Lymphocyte Stimulator) but not, biotinylated BLySB Lymphocyte Stimulator (bio-BLySB Lymphocyte Stimulator) or an uncoated well (PBS). This indicates that the scFvs recognize the membrane-bound form of BLySB Lymphocyte Stimulator.

Example 16: Specificity for Membrane-bound BLySB Lymphocyte Stimulator

[0733] The specificity of the scFvs for only the membrane-bound form of BLySB Lymphocyte Stimulator, and not for the soluble form, was confirmed using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of BLySB Lymphocyte Stimulator on U937 plasma membranes in the presence of different forms of competing BLySB Lymphocyte Stimulator. Competing BLySB Lymphocyte Stimulator was either the His-tagged form of BLySB Lymphocyte Stimulator or soluble BLySB Lymphocyte Stimulator. ScFvs specific for the membrane-bound

BLySB Lymphocyte Stimulator would be expected to be competed out by pre-incubation with His-tagged BLySB Lymphocyte Stimulator but not by pre-incubation with soluble BLySB Lymphocyte Stimulator.

[0734] Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

Competition ELISA

[0735] U937 plasma membranes (50µl per well) were coated at 10µg/ml in PBS onto Falcon 96-well plates overnight at 4°C.

[0736] Individual E. coli colonies containing a phagemid representing one of the unique scFvs from the panel 3 were inoculated into 50 ml tubes (Falcon) containing 5 ml 2TYAG medium. Tubes were incubated at 37°C for 4 hours, shaking. M13KO7 helper phage was added to each tube to an MOI of 10 and the tubes were incubated for a further 1 hour at 37°C. The tubes were centrifuged in a benchtop centrifuge at 3500 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 5 ml 2TYAK and incubated at 30°C overnight, shaking. The next day, tubes were centrifuged at 3500 rpm for 10 min and the phage-containing supernatant carefully transferred into a fresh tube.

[0737] For each test phage antibody, 3 aliquots of 20µl 18% marvel/6xPBS were transferred into separate wells of a 96-well plate. The first aliquot was supplemented with His-tagged BLySB Lymphocyte Stimulator to a final concentration of 60 µg/ml. The second aliquot was supplemented with soluble BLySB Lymphocyte Stimulator to a final concentration of 60 µg/ml. The third aliquot was not supplemented with any competing antigen. One hundred µl of phage supernatant was then added to each aliquot and left to block at room temperature for 1 hour.

[0738] The antigen-coated plates were washed once with PBS before the addition of 200 µl/well 3% marvel/PBS. These plates were left to block at 37°C for 1 hour and were then washed once with PBS. Duplicate samples of 50 µl pre-blocked phage (above) were added to the antigen-coated plates and left at room temperature for 1 hour. Plates were washed 3x with PBS/0.1%Tween 20, then 3x with PBS. Fifty µl/well mouse anti-M13 HRP (Pharmacia) at 1/5000 in 3% Marvel/PBS was added and left for 1 hour at room temperature. Plates were washed 3 times with PBS/0.1%Tween 20, then 3 times with PBS.

Fifty μl /well HRP-labelled anti-mouse Envision polymer (DAKO) at 1/50 in 3% marvel/PBS was added and left for 1 hour at RT. Plates were washed 3 times with PBS/0.1% Tween 20, then 3 times with PBS. Next, 50 μl /well of TMB (Sigma) was added and plates left to develop for 30 to 60 minutes. When sufficient color has developed, 25 μl /well 0.5M H_2SO_4 was added to stop the reaction. The plates were read at 450nm on a microtiter plate reader (Bio-Rad 3550).

[0739] The results for 3 clones, I079B04, I079F08 and I080B01, and a control phage antibody that recognizes $\text{TNF}\alpha$, are shown in Figure 13. All 3 scFvs recognize U937 plasma membranes (U937). This binding is competed out to background levels (i.e. comparable to the signal observed with the anti- $\text{TNF}\alpha$ phage antibody) in the presence of His-tagged BLySB Lymphocyte Stimulator (HIS-BLySB Lymphocyte Stimulator) but not biotinylated BLySB Lymphocyte Stimulator (bio-BLySB Lymphocyte Stimulator). This confirms that the scFvs specifically recognize the membrane-bound form but not the soluble form of BLySB Lymphocyte Stimulator.

Example 17: High Throughput BIAcore Screen to identify high affinity scFvs

[0740] This is a 96-well screen where the test samples (scFvs) are derived from 1 ml periplasmic extracts of individual antibody expressing clones. Potentially higher affinity scFvs are then identified principally as those giving a large number of total RU's bound to a HIS-BLySB Lymphocyte Stimulator surface in BIAcore. This method of ranking does assume approximately equal yields of scFv from each clone. Since this is not always the case, some scFvs may also be identified that simply express high levels of scFv. These can be discriminated from those of higher affinity by further characterization of the scFvs (see Example 18).

Preparation of ScFv from 1ml E.coli Cultures

[0741] Individual E.coli colonies containing a phagemid representing one of the unique scFvs from panel 3 were inoculated into 96-well plates containing 100 μl 2TYAG medium per well. Eight wells on each plate were reserved for positive and negative control samples. The plate was grown overnight at 30°C with shaking at 120 rpm.

[0742] Next day, 1ml of 2TYAG + 345 mM sucrose was added to each well of an autoclaved 96 deep well plate (Beckman). Twenty μl of each overnight culture was

resuspended and transferred to the appropriate well of the deep well plate. The plate was grown for approximately 3.5 hours at 30°C with shaking at 250 rpm (or until the OD₆₀₀ = 0.6). Fifty µl of 1M IPTG was added to 5ml 2TY and 10µl of this was added to each well. The plate was grown overnight at 30°C with shaking at 250rpm.

[0743] Plates were kept at 4°C for the remainder of the procedure. The overnight plate (above) was centrifuged at 3500 rpm for 10 minutes at 4°C to pellet the cells. The supernatant was decanted and each pellet resuspended in 100µl TES (0.2M Tris HCl pH8.0, 0.5mM EDTA, 0.5M sucrose) and transferred to a fresh 96 well plate. This plate was incubated on ice for 30 minutes and then centrifuged for 10 minutes at 3500 rpm at 4°C to pellet the cell debris. During centrifugation, 15µl of freshly made protease inhibitors cocktail (Roche, 1 tablet dissolved in 1.5 ml water) was added to each well of a fresh 96 well plate. Supernatants from the centrifuged plate were then transferred to the plate containing the protease inhibitors. The plate was centrifuged at 3500 rpm for 10 minutes at 4°C and the supernatant was transferred to a further 96-well plate. This step was repeated at least once more or until there was no sign of any cell debris following centrifugation. Finally, the plate was covered in foil to prevent evaporation of samples during the BIAcore run.

Generation of a high density HIS-BLySB Lymphocyte Stimulator surface

[0744] All BIAcore analysis was performed on BIAcore 2000 machines, using the BIAcore 2000 control software and evaluated using the BIAevaluation 3.0 software. A high density His-tagged BLySB Lymphocyte Stimulator surface (>1000 RU HIS-BLySB Lymphocyte Stimulator coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram started over flow cell 2 with HBS buffer at a flow rate of 5µl/min. The NHS and EDC solution were mixed 1:1 before injecting 30µl over the CM5 surface. Fifty µl HIS-BLySB Lymphocyte Stimulator (at 10µg/ml in Sodium acetate buffer, pH4) was injected and allowed to couple to the surface. Thirty µl of ethanolamine-HCl solution was then injected to block free NHS esters. Prior to using the chip, 10µl of 4M Guanidine hydrochloride in HBS was injected over the surface to strip the surface of non-covalently bound BLySB Lymphocyte Stimulator. A blank surface (no HIS-BLySB Lymphocyte Stimulator) was also prepared

over flow cell 1 so that non-specific binding effects can be subtracted from the HIS-BLySB Lymphocyte Stimulator binding curves.

[0745] Typically, a 5000 RU His-tagged BLySB Lymphocyte Stimulator surface was generated in this way and used for 96-well analysis of scFvs isolated from the periplasm of E.coli.

BIACore Analysis

[0746] The 96-well plate containing periplasmic scFvs was secured inside the BIAcore. Two ml of 4M Guanidine hydrochloride in HBS was placed in a rack inside the BIAcore for regeneration of the HIS-BLySB Lymphocyte Stimulator surface between samples. The sensorgram was run over flow cells 1 and 2 at a flow rate of 20µl/minute. The following method was run:

MAIN

FLOWCELL 1,2,3,4

LOOP cycle STEP

APROG inj %pos

ENDLOOP

APPEND CONTINUE

END

DEFINE LOOP cycle

LPARAM %pos

r1a1

r1b1

r1c1

r1d1

r1e1

r1f1 etc (all wells listed until r1h12)

```

END
DEFINE APROG inj
PARAM %pos
FLOW 20
KINJECT %pos 35 30 !scfv injection
QUICKINJECT r2f3 10 !regeneration
EXTRACLEAN
END

```

[0747] When the run had finished, the sensorgram data for flow cell 1 was subtracted from the data for flow cell 2 for each sample using the BIAevaluation software. The clones were compared with one another principally by overall RU change as the scFv dissociates from the surface. In addition a few scFvs were identified as having potentially slower off-rates. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in Figure 14. An anti-TNF α antibody that does not recognize BLySB Lymphocyte Stimulator was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

[0748] ScFvs were identified principally if they demonstrated a RU change of over 1200, a few were also identified as having potentially slower than typical off-rates. A total of 28 clones were chosen on these criteria and are listed in Table 7.

Table 7: Identification of 28 antibodies to membrane-bound BLySB Lymphocyte Stimulator that demonstrate the most significant RU changes by BIAcore

Antibody	Antibody
I079C01	I084C04
I082H08	I080E05
I079E02	I083B12
I079B05	I082G01
I079F06	I082G02
I079F08	I082C03
I079F11	I082A05

I079B12	I082D07
I080B01	I082B08
I080G09	I084A01
I099D03	I084B02
I080D03	I080A08
I080A03	I084C11
I083G03	
I080G07	

Example 18: scFv Affinity Determinations

[0749] The affinity (K_D) of the 28 scFvs was determined using the BIAcore.

Low Density HIS-BLySB Lymphocyte Stimulator Surface for Kinetic Studies

[0750] 500RU surfaces were used for kinetic studies of purified scFv binding to HIS-BLySB Lymphocyte Stimulator. The method to prepare these surfaces was identical to the method described in Example 17, only smaller volumes of HIS-BLySB Lymphocyte Stimulator were injected.

Measurement of scFv Binding Kinetics

[0751] The chip containing the low density HIS-BLySB Lymphocyte Stimulator surface was inserted into the BIAcore. A dilution series for each of the 28 purified scFvs (prepared as in Example 6) were diluted in HBS (typically starting with 50µg/ml scFv and double diluting down to 1.5µg/ml). The dilution series was then injected sequentially over the blank control (flow cell 1) and low density HIS-BLySB Lymphocyte Stimulator surface (flow cell 2) using the following program:

MAIN

FLOWCELL 1,2,3,4

APROG	genab	r1d1	ab1
APROG	genab	r1d2	ab2
APROG	genab	r1d3	ab3
APROG	genab	r1d4	ab4
APROG	genab	r1d5	ab5
APROG	genab	r1d6	ab6

APPEND CONTINUE

END

DEFINE APROG genab

PARAM %Abpos %AbId

FLOW 20

KINJECT %Abpos 200 80

INJECT r2f3 10

EXTRACLEAN

END

[0752] Bound scFv were removed by injecting 10µl of 4M Guanidine hydrochloride in HBS (location r2f3 in the above program) over the surface between samples. Binding curves for individual scFv were analysed using the BIAevaluation software to determine antibody on- and off-rates.

[0753] A typical example of the binding curves generated for the scFv antibody I082C03 is shown in Figure 15. The off-rate for this clone was calculated as $2 \times 10^{-3} \text{ s}^{-1}$. The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv. The 5 scFvs with the highest affinities as scFvs are given in Table 8.

Table 8: Identification of 5 antibodies to membrane-bound BLySB Lymphocyte Stimulator that have the highest affinities as scFvs

Antibody	Affinity (K _D)
I079F11	5nM
I079E02	10nM
I082G02	6nM
I082H08	1nM
I099D03	4nM

Example 19: Recognition of mouse membrane-bound BLySB Lymphocyte Stimulator

[0754] The ability of the 5 scFvs listed in Table 8 to also recognize murine membrane-bound BLySB Lymphocyte Stimulator was determined using a competition

ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of BLySB Lymphocyte Stimulator on the murine cell line, P388, plasma membranes in the presence of different forms of competing human BLySB Lymphocyte Stimulator. Competing BLySB Lymphocyte Stimulator was either presented as the His-tagged form of BLySB Lymphocyte Stimulator, or soluble BLySB Lymphocyte Stimulator. ScFvs that recognize mouse membrane-bound BLySB Lymphocyte Stimulator would give an ELISA signal on the P388 plasma membranes that is competed out by pre-incubation with HIS-tagged BLySB Lymphocyte Stimulator but not by pre-incubation with soluble BLySB Lymphocyte Stimulator.

Maintenance of P388.D1 cells and preparation of plasma membranes

[0755] P388.D1 cells are a mouse monocyte-macrophage like cell line. They were cultured in L-15 medium supplemented with 2mM L-glutamine, 10% CS, 10U penicillin, 100g/ml streptomycin (all reagents from Sigma). Cells were split 1:4 every 3-4 days to maintain a cell density of $2-8 \times 10^5$ per ml. A fresh aliquot of cells was thawed from liquid nitrogen every 6 weeks. Plasma membrane fractions were prepared as described in Example 2.

Competition ELISA

[0756] P388 plasma membranes (50µl per well) were coated at 10µg/ml in PBS onto Falcon 96-well plates overnight at 4°C. The method is otherwise essentially as described Example 16.

[0757] The results for 3 clones, I079E02, I082H08 and I099D03 are shown in Figure 16. All 3 scFvs recognize P388 plasma membranes. This binding is competed out in the presence of HIS-tagged BLySB Lymphocyte Stimulator (HIS-BLySB Lymphocyte Stimulator) but not in the presence of biotinylated BLySB Lymphocyte Stimulator (bio-BLySB Lymphocyte Stimulator). This confirms that these scFvs also recognize the membrane-bound form but not the soluble form of mouse BLySB Lymphocyte Stimulator.

Example 20 : Conversion of scFvs to IgG1 format

[0758] The VH domain and the VL domains of scFvs that we wished to convert into IgG molecules were cloned into vectors containing the nucleotide sequences of the

appropriate heavy (human IgG1) or light chain (human kappa or human lambda) constant regions such that a complete heavy or light chain molecule could be expressed from these vectors when transfected into an appropriate host cell. Further, when cloned heavy and light chains are both expressed in one cell line (from either one or two vectors), they can assemble into a complete functional antibody molecule that is secreted into the cell culture medium. Methods for converting scFvs into conventional antibody molecules are well known within the art.

Generation of NS0 cell lines expressing anti-BLySB Lymphocyte Stimulator antibodies (IgG1)

[0759] Plasmids containing the heavy and light chains were separately linearized using the Pvu I restriction enzyme. The linearized DNAs were purified by phenol-chloroform extraction followed by ethanol precipitation and then resuspended in H₂O. NS0 cells (10⁷) from a growing culture were electroporated (0.25kV and 975μF) in PBS with 12.5 μg linearized heavy chain plasmid DNA and 37.5 μg linearized light chain DNA. The cells were washed in 20 ml non-selective medium (10% FCS in DMEM supplemented with 6mM glutamine, amino acids and penicillin/streptomycin) and then transferred in 12.5 ml medium into a T75cm² flask and incubated overnight at 37°C, 5% CO₂/air. The day after transfection the cells were resuspended in selective medium containing 1mg/ml geneticin and dispensed into 5 x 96-well plates at 200 μl/well. After 18 days at 37°C (5% CO₂/air) the colony supernatants were screened by an ELISA that detects assembled human IgG in order to identify colonies expressing IgG. Approximately twenty positive colonies were expanded and adapted to growth in serum-free, selective medium. Duplicate T25cm² flasks were set up. Cells from one flask were frozen down as a stock and cells in the second flask were grown to saturation. The productivity of the saturated cultures was assessed by ELISA. The highest producing cell lines were then selected for large-scale antibody production.

[0760] The above procedure is exemplified for the I006D08 anti-BLySB Lymphocyte Stimulator antibody constructs. Following electroporation and selection of NS0 cells, supernatants from ninety-three wells each containing a single colony were screened by ELISA to detect assembled IgG1, antibody. Twenty-seven of the supernatants were identified as containing IgG. The colonies from 24 of the positive wells

were transferred to 1ml selective medium in a 24-well plate and allowed to grow for 2 days. The 1ml cultures of cells were then added to 4ml selective medium containing reduced serum (0.5% FCS) in a T25cm² flask. When the cultures reached confluency 1 ml cells were diluted in 4ml selective, serum-free medium in a T25cm² flask. At confluency this subculture regime was repeated again. Finally 1ml cells from the culture containing 0.1% FCS was diluted with 9 ml serum-free, selective medium and divided into 2 x T25cm² to form the saturated and stock cultures. The stock cultures were frozen down and stored in liquid nitrogen once the cultures were confluent. The saturation culture was grown until the viability of the culture was < 10%. Twenty-three out of the 24 colonies originally expanded were successfully adapted to growth in serum-free medium. The productivity of these serum-free adapted cell lines ranged from 0.3 to 17 µg/ml by ELISA quantification of the saturated, 5ml serum-free cultures. The I006D08-32 cell line produced 17 µg/ml.

Large-scale IgG production

[0761] The highest-producing cell lines were revived from frozen stocks and then expanded to 400ml in selective, serum-free medium in 2 liter roller bottles. The cells were grown at 37°C and rolled at 4 rpm with the headspace being re-equilibrated with 5% CO₂/air every 2-3 days. Finally the culture was expanded to a 4 liter volume by the addition of serum-free medium without selection (400 ml per 2 liter roller bottle). The cultures were then grown to saturation.

[0762] This procedure is exemplified by the production of I006D08 antibody from the I006D08-32 cell line. The frozen stock of I006D08-32 was revived into a T25 cm² containing 5 ml serum-free medium containing 1mg/ml geneticin and grown at 37°C in 5% CO₂/air incubator. After two days growth the culture was diluted with 7.5 ml fresh medium and transferred to a T75cm² flask. After a further three days in the incubator the cells were transferred to 130 ml selective medium and transferred to a 2 liter roller bottle. After three days growth the cells were diluted with 500 ml selective medium and split into 2 x 2 liter roller bottles. After another 2 days 100 ml fresh selective medium was added to each roller. Finally the next day the culture was expanded to a total volume of 4 liters with non-selective medium and divided into 10 x 2 liter roller bottles. After three days the medium was supplemented with 6mM glutamine. The cells were grown for 17 days from

the final subculture into a 4 liter volume. The cells grew up to 3×10^6 cells/ml before viability declined to $< 0.2 \times 10^6$ cells/ml. At this low viability the culture supernatants were harvested. ELISA analysis indicated that the culture supernatant contained 33 $\mu\text{g/ml}$ IgG. Hence, the 4 liter culture contained 132 mg IgG.

IgG Purification

[0763] The purification of the IgG from the fermentation broth is performed using a combination of conventional techniques commonly used for antibody production. Typically the culture harvest is clarified to remove cells and cellular debris prior to starting the purification scheme. This would normally be achieved using either centrifugation or filtration of the harvest. Following clarification, the antibody would typically be captured and significantly purified using affinity chromatography on Protein A Sepharose. The antibody is bound to Protein A Sepharose at basic pH and, following washing of the matrix, is eluted by a reduction of the pH. Further purification of the antibody is then achieved by gel filtration. As well as removing components with different molecular weights from the antibody this step can also be used to buffer exchange into the desired final formulation buffer.

Purification of I006D08 IgG1

[0764] The harvest was clarified by sequential filtration through 0.5 μm and 0.22 μm filters. Clarified harvest was then applied to a column of recombinant Protein A Sepharose equilibrated at pH 8.0 and washed with the equilibration buffer. I006D08 antibody was eluted from the Protein A Sepharose by application of a buffer at pH 3.5. The collected antibody containing eluate was then neutralized to pH 7.4 by the addition of pH 8.0 buffer. The neutralized eluate was concentrated by ultrafiltration using a 30 KDa cut off membrane. Concentrated material was then purified by Sephacryl S300HR gel filtration using phosphate buffered saline as the mobile phase. The final monomeric IgG1 fraction from the gel filtration column was then concentrated to the desired formulation concentration by ultrafiltration using a 30 KDa cut off membrane. The final product was filtered through a 0.22 μm filter.

Example 21: Antibody neutralization of murine splenocyte proliferation as measured by ³HdT incorporation

[0765] To determine if an antibody inhibited BLySB Lymphocyte Stimulator mediated B cell proliferation, a splenocyte proliferation assay was performed. Briefly, murine splenocytes were isolated by flushing spleen with complete medium using a 25g needle and 10 ml of complete medium (RPMI 1640 with 10% FBS containing 100U/ml penicillin, 100µg/ml streptomycin, 4mM glutamine, 5x10⁻⁵M β-mercaptoethanol). The cells were passed through a 100 micron nylon filter to remove cell clumps. The cell suspension was then ficolled at 400 x g for 25 minutes at room temperature (one 15 ml conical tube/spleen; 3 ml ficol, 10 ml cell suspension/spleen; Ficoll 1083 from Sigma). The recovered cells were washed 3 times in complete medium and counted. Recovered cells were then diluted to a concentration of 3x10⁶/ml in complete medium containing a 3X concentration of SAC (3X = 1:33,333 dilution of stock) (Staph. aureus Cowan strain; Calbiochem).

[0766] For each antibody, 50 microliters of antibody dilutions at 30µg/ml, 3.0µg/ml, and 0.3µg/ml concentrations were aliquotted into individual wells of a 96 well plate in triplicate. Suitable positive controls, such as, for example monoclonal antibody 15C10, were also used. Medium containing no antibody (and human isotype controls (purchased commercially) when necessary) were used as negative controls.

[0767] BLySB Lymphocyte Stimulator protein was diluted in complete medium to concentrations of 300ng/ml, 90ng/ml and 30ng/ml. 50 microliters of each of the BLySB Lymphocyte Stimulator dilutions were then added to the antibody dilution series in the plates. The plate containing the antibody and BLySB Lymphocyte Stimulator dilutions are then incubated for 30 minutes at 37°C, 5% CO₂, after which 50 microliters of the splenocyte cell suspension containing SAC was added to all wells. The plates were then incubated for 72 hours (37°C, 5% CO₂).

[0768] After 72 hours, each well was supplemented with 50µl of complete medium containing 0.5µCi of ³H-thymidine (6.7 Ci/mM; Amersham) and cells were incubated for an additional 20-24 hours at (37°C, 5% CO₂). Following incubation cells were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

Example 22: Human B cell proliferation assay for in vitro screening of BLySB
Lymphocyte Stimulator antagonist molecules

[0769] The bioassay for assessing the effects of putative BLySB Lymphocyte Stimulator antagonists was performed in triplicate in 96 well format by mixing equal volumes of BLySB Lymphocyte Stimulator, responder cells, and putative antagonist each of which is prepared as a 3X stock reagent.

[0770] B-lymphocytes were purified from human tonsil by MACS (anti-CD3 depletion), washed, and resuspended in complete medium (CM) (RPMI 1640 with 10% FBS containing 100U/ml penicillin, 100µg/ml streptomycin, 4mM glutamine, 5x10E-5 M beta-mercaptoethanol) at a concentration of 3 x 10⁶ cells/mL. *Staphylococcus aureus*, Cowan I (SAC, CalBiochem) was added to cells at 3X concentration (3X = 1:33,333 dilution of stock

[0771] Meanwhile, eight serial dilutions (3-fold) of potential antagonist were prepared in CM such that the diluted antagonists are at 3X the final concentrations to be tested in the assay. Antibodies are routinely tested starting at a final concentration of 10ug/mL and going down to about 1.5 ng/mL.

[0772] Human rBLySB Lymphocyte Stimulator was prepared in CM to 3X concentration (3X = 300 ng/mL, 30 ng/mL, and 3 ng/mL) in CM. Potential inhibitors were routinely tested at several concentrations of BLySB Lymphocyte Stimulator to avoid false negatives due to unexpectedly low affinity or antagonist concentration.

[0773] Fifty microliters of diluted antagonist and 50uL of diluted BLySB Lymphocyte Stimulator were added to the putative antagonist dilution series.

[0774] Cells were then incubated for 72 hours (37°C, 5% CO₂) in a fully humidified chamber. After 72 hrs., the cells were supplemented with 0.5 µCi/well 3H-thymidine (6.7 Ci/mmol) and incubated for an additional 24 hours. Plates were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

[0775] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in this application is incorporated in their entireties herein by reference. Further, the sequences disclosed herein are also disclosed in U.S. Provisional Application 60/212,210 filed June 16, 2000 the contents of which are incorporated in their entireties herein by reference.

Table 1: scFvs that Immunospecifically Bind to BLySB Lymphocyte Stimulator

Table 1-scFvs that Immunospecifically Bind to BLyS

Clone ID	seFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
1003F12S	1	138 - 248	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	HDDDVLTGYFES (SEQ ID NO: 2130)
1006D08	2	139 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	SRDLLLPHYGMDV (SEQ ID NO: 2133)
1008A11	3	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	DYDILTYGYYGMDV (SEQ ID NO: 2129)
1017D10	4	148 - 255	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	VQMDSYYDLTGINVGPPYFDY (SEQ ID NO: 2132)
1022D01	5	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	DGYDILTYGYYGMDV (SEQ ID NO: 2135)
1031F02	6	137 - 251	137 - 251	160 - 173	189 - 195	228 - 240	1 - 121	26 - 35	50 - 66	GYDSSAFRAFDI (SEQ ID NO: 2136)
1050A12	7	140 - 250	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 35	50 - 66	APYDLLTHYFHYFDY (SEQ ID NO: 2134)
1051C04	8	145 - 256	145 - 256	168 - 181	197 - 203	236 - 245	1 - 129	26 - 35	50 - 66	AATTSQKHNYAYFYGMDV (SEQ ID NO: 2131)
1050B11	9	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2137)
1050B11-01	10	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2137)
1050B11-02	11	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2143)
1050B11-03	12	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2144)
1050B11-04	13	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2141)
1050B11-05	14	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2142)
1050B11-06	15	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2140)
1050B11-07	16	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2144)
1050B11-08	17	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2141)
1050B11-09	18	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2142)
1050B11-10	19	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2142)
1050B11-11	20	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2140)
1050B11-12	21	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2140)
1050B11-13	22	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2137)
1050B11-14	23	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2137)
1050B11-15	24	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2143)
1050B11-16	25	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2143)
1050B11-17	26	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2144)
1050B11-18	27	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2144)
1050B11-19	28	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)
1050B11-20	29	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)
1050B11-21	30	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2138)
1050B11-22	31	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2138)
1050B11-23	32	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)
1050B11-24	33	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)
1050B11-25	34	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2144)
1050B11-26	35	141 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	PFYDILTSYVFQYFDH (SEQ ID NO: 2139)

1087G06	78	<u>140142</u> - 250	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDILTTSYVHPSPRS (SEQ ID NO: 2285)
1087G07	79	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVLRPPQ (SEQ ID NO: 2241)
1087G09	80	<u>140142</u> - 250	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDILTTSYVGPYGT (SEQ ID NO: 2284)
1087G10	81	<u>140142</u> - 250	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDILTTSYVTPCT (SEQ ID NO: 2276)
1087H02	82	<u>137</u> - 244	137 - 244	160 - 170	186 - 192	225 - 233	1 - 121	26 - 35	50 - 66	99 - 110	ASYLETSSSLDN (SEQ ID NO: 2265)
1088A01	83	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088A03	84	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVIPFLPL (SEQ ID NO: 2290)
1088A04	85	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVLHIYPH (SEQ ID NO: 2335)
1088A08	86	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTNYVFEYYAS (SEQ ID NO: 2323)
1088A09	87	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVILYYLH (SEQ ID NO: 2295)
1088A10	88	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088A11	89	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVLMYFPH (SEQ ID NO: 2220)
1088A12	90	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVLLFFYPL (SEQ ID NO: 2325)
1088B01	91	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088B02	92	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFEDYYAS (SEQ ID NO: 2244)
1088B03	93	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVIPFLPL (SEQ ID NO: 2290)
1088B05	94	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088B06	95	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFEYYSL (SEQ ID NO: 2324)
1088B07	96	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088B08	97	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088B09	98	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVLEFYLL (SEQ ID NO: 2303)
1088B10	99	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088B12	100	<u>140142</u> - 250	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDILTTSYVLPDLS (SEQ ID NO: 2223)
1088C01	101	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVLYFYPS (SEQ ID NO: 2317)
1088C03	102	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088C09	103	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088C12	104	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088D01	105	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088D03	106	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088D04	107	<u>140142</u> - 250	140 - 250	165 - 176	192 - 198	231 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PFYDILTTSYVLPSPV (SEQ ID NO: 2225)
1088D07	108	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088D08	109	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088E01	110	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088E02	111	<u>138140</u> - 248	138 - 248	163 - 174	190 - 196	229 - 237	1 - 122	23 - 32	47 - 63	96 - 111	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088E03	112	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVLPSPV (SEQ ID NO: 2225)
1088E04	113	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFEYYSL (SEQ ID NO: 2324)
1088E08	114	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088E10	115	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088E11	116	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088E13	117	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088F07	118	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)
1088G02	119	<u>141143</u> - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTTSYVFQYFDH (SEQ ID NO: 2137)

1092G05	162	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1092G10	163	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1092H01	164	137 - 244	137 - 244	160 - 170	186 - 192	225 - 233	1 - 121	26 - 35	50 - 66	99 - 110	ASYLSTSSSLDN (SEQ ID NO: 2265)
1093A06	165	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLPVYDH (SEQ ID NO: 2334)
1093A09	166	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFAH (SEQ ID NO: 2268)
1093A11	167	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093A12	168	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093B02	169	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093B05	170	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093B06	171	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093B09	172	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEVYHP (SEQ ID NO: 2318)
1093B12	173	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEVYHP (SEQ ID NO: 2242)
1093C02	174	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEHAYAF (SEQ ID NO: 2332)
1093C03	175	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093C05	176	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVILYYLH (SEQ ID NO: 2295)
1093D05	177	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFEFLPL (SEQ ID NO: 2245)
1093D08	178	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVRPFYAH (SEQ ID NO: 2273)
1093D10	179	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093D12	180	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLFHFRV (SEQ ID NO: 2302)
1093E01	181	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093E02	182	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIQYFDH (SEQ ID NO: 2297)
1093E05	183	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVHEFSL (SEQ ID NO: 2283)
1093E08	184	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVMQFPT (SEQ ID NO: 2321)
1093E10	185	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLSFPV (SEQ ID NO: 2246)
1093F01	186	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLYYAF (SEQ ID NO: 2251)
1093F03	187	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093F05	188	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093F08	189	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093F11	190	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLFHFPYPL (SEQ ID NO: 2333)
1093G07	191	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLYYVVL (SEQ ID NO: 2237)
1093G11	192	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093G12	193	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1093H06	194	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1094A08	195	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDY (SEQ ID NO: 2280)
1094B07	196	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLPVWVS (SEQ ID NO: 2228)
1094B08	197	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1094B12	198	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1094C11	199	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1094C12	200	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1094D06	201	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVIEYYPV (SEQ ID NO: 2288)
1094D07	202	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVFQYFDH (SEQ ID NO: 2137)
1094D08	203	141-143 - 251	141 - 251	166 - 177	193 - 199	232 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PFYDTLTSYVLEHVLPL (SEQ ID NO: 2314)

288	1098G02	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
289	1098G12	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
290	1098H05	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
291	1101A01	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
292	1101B04	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
293	1101B06	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
294	1101D04	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVLEFPD (SEQ ID NO: 2313)
295	1101D07	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
296	1101E09	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDR (SEQ ID NO: 2279)
297	1101E12	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
298	1101G02	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
299	1101G11	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
300	1102C03	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
301	1102E09	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
302	1102F02	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
303	1102G08	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
304	1102G09	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVHLVYAH (SEQ ID NO: 2214)
305	1106A09	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
306	1106B02	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
307	1106B06	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
308	1106C07	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
309	1106E05	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
310	1106E12	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
311	1106G01	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
312	1106G03	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
313	1109B06	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
314	1109D12	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
315	1109E12	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
316	1109G06	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
317	1109H04	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
318	1111B03	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
319	1111D09	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
320	1111D21F10	141 143-251	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDRLTSYVVFQYFDH (SEQ ID NO: 2137)
321	1089F12	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHGLDV (SEQ ID NO: 2151)
322	1103E12	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHGLDS (SEQ ID NO: 2146)
323	1108D08	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSFDL (SEQ ID NO: 2147)
324	1108E06	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPLAPLYP (SEQ ID NO: 2148)
325	1113E07	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHGLDV (SEQ ID NO: 2151)
326	1114G05	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSIDL (SEQ ID NO: 2152)
327	1116A01	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSFLP (SEQ ID NO: 2149)
328	1116A09	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRVLLLLPPHHSFDL (SEQ ID NO: 2150)
329	116C11	139 141-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSFDL (SEQ ID NO: 2147)

1085A01	330	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHDHLF (SEQ ID NO: 2602)
1085A02	331	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSDPLGF (SEQ ID NO: 2639)
1085A03	332	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPTHPLSF (SEQ ID NO: 2561)
1085A04	333	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPLAPLFF (SEQ ID NO: 2550)
1085A05	334	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSDPLSL (SEQ ID NO: 2659)
1085A06	335	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFAPSAPLSF (SEQ ID NO: 2611)
1085A07	336	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFAPSAPLSF (SEQ ID NO: 2390)
1085A09	337	<u>138140</u> - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLFPNDALS (SEQ ID NO: 2632)
1085A10	338	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFAPSAPLRF (SEQ ID NO: 2609)
1085A11	339	<u>138140</u> - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLPHDPLE (SEQ ID NO: 2363)
1085B01	340	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQSLYP (SEQ ID NO: 2466)
1085B02	341	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSSLVF (SEQ ID NO: 2392)
1085B03	342	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYDPLLF (SEQ ID NO: 2638)
1085B04	343	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLYF (SEQ ID NO: 2589)
1085B05	344	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLSP (SEQ ID NO: 2573)
1085B06	345	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPLSPLSF (SEQ ID NO: 2574)
1085B07	346	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPDFPMAP (SEQ ID NO: 2433)
1085B10	347	<u>138140</u> - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLFPHSPLY (SEQ ID NO: 2470)
1085B12	348	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQDPLSP (SEQ ID NO: 2372)
1085C02	349	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPDPLLS (SEQ ID NO: 2430)
1085C03	350	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHGPLLI (SEQ ID NO: 2400)
1085C05	351	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPGSPLLF (SEQ ID NO: 2491)
1085C06	352	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTAALSF (SEQ ID NO: 2341)
1085C07	353	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHPTPLRF (SEQ ID NO: 2375)
1085C09	354	<u>138140</u> - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLFPHSPLT (SEQ ID NO: 2468)
1085C10	355	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPLLF (SEQ ID NO: 2471)
1085C12	356	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPLLF (SEQ ID NO: 2680)
1085D01	357	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRPLLF (SEQ ID NO: 2548)
1085D02	358	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSQYLDLF (SEQ ID NO: 2523)
1085D03	359	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFSSPLLF (SEQ ID NO: 2713)
1085D04	360	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYPLVF (SEQ ID NO: 2646)
1085D06	361	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLLD (SEQ ID NO: 2488)
1085D07	362	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLLF (SEQ ID NO: 2694)
1085D08	363	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSYLSP (SEQ ID NO: 2477)
1085D09	364	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQPLFP (SEQ ID NO: 2467)
1085D10	365	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPLHP (SEQ ID NO: 2563)
1085D11	366	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLAP (SEQ ID NO: 2510)
1085D12	367	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHTLRF (SEQ ID NO: 2495)
1085E01	368	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYAVLHF (SEQ ID NO: 2620)
1085E02	369	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTSPLRL (SEQ ID NO: 2575)
1085E07	370	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFSDALS (SEQ ID NO: 2568)
1085E08	371	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAPLDP (SEQ ID NO: 2603)

1085E09	372	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHDP	PRF (SEQ ID NO: 2628)
1085E10	373	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSEPL	WP (SEQ ID NO: 2668)
1085E11	374	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSSPL	SN (SEQ ID NO: 2716)
1085E12	375	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHPLTP	(SEQ ID NO: 2431)
1085F01	376	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSP	LLF (SEQ ID NO: 2551)
1085F02	377	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSP	LQL (SEQ ID NO: 2376)
1085F03	378	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPYTP	LLF (SEQ ID NO: 2682)
1085F04	379	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSSPL	AF (SEQ ID NO: 2707)
1085F05	380	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHDPL	YF (SEQ ID NO: 2706)
1085F06	381	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SAHLF (SEQ ID NO: 2586)
1085F07	382	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPAG	PLRF (SEQ ID NO: 2410)
1085F09	383	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPDHAF	FFV (SEQ ID NO: 2439)
1085F10	384	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSSD	GFA (SEQ ID NO: 2662)
1085F11	385	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSSY	LEF (SEQ ID NO: 2339)
1085F12	386	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRDPL	LI (SEQ ID NO: 2558)
1085G01	387	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SAPLHP (SEQ ID NO: 2605)
1085G02	388	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	NAPLLL (SEQ ID NO: 2613)
1085G03	389	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	APLLF (SEQ ID NO: 2403)
1085G04	390	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SAPLDP (SEQ ID NO: 2601)
1085G07	391	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	NAVLDI (SEQ ID NO: 2629)
1085G08	392	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SEPLFF (SEQ ID NO: 2664)
1085G09	393	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SSVLP (SEQ ID NO: 2338)
1085G10	394	<u>138140</u> - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLP	HAPLQ (SEQ ID NO: 2554)
1085G11	395	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SDSLAP (SEQ ID NO: 2445)
1085G12	396	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SSPLHP (SEQ ID NO: 2576)
1085H10	397	<u>142141</u> - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYYDILTGY	SYGMDV (SEQ ID NO: 2135)
1086A03	398	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SMP
1086A04	399	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SHLHP (SEQ ID NO: 2438)
1086A05	400	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	HAPLSH (SEQ ID NO: 2569)
1086A07	401	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	DAALRF (SEQ ID NO: 2421)
1086A09	402	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SSHLF (SEQ ID NO: 2704)
1086A10	403	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SAPLSS (SEQ ID NO: 2624)
1086A11	404	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	HAPLTP (SEQ ID NO: 2577)
1086A12	405	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	YDPLHS (SEQ ID NO: 2635)
1086B02	406	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	PHPLHP (SEQ ID NO: 2348)
1086B03	407	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	HAPLFF (SEQ ID NO: 2412)
1086B05	408	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	PFPEPLII (SEQ ID NO: 2457)
1086B06	409	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	ASPLNP (SEQ ID NO: 2364)
1086B07	410	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	SSPLYF (SEQ ID NO: 2720)
1086B09	411	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	TSPLSF (SEQ ID NO: 2579)
1086B10	412	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	DDGLSS (SEQ ID NO: 2428)
1086B11	413	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLP	ISP

1086C03	414	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPPTAPLYG (SEQ ID NO: 2535)
1086C05	415	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHHSLLF (SEQ ID NO: 2427)
1086C07	416	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQPLRF (SEQ ID NO: 2440)
1086C08	417	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFAAPLAF (SEQ ID NO: 2401)
1086C09	418	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHPLLF (SEQ ID NO: 2350)
1086C10	419	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPPTPLIF (SEQ ID NO: 2541)
1086C11	420	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPDDPLSF (SEQ ID NO: 2432)
1086C12	421	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPPTDLSLF (SEQ ID NO: 2622)
1086D01	422	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFAPSAPLTP (SEQ ID NO: 2630)
1086D04	423	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYAPLYD (SEQ ID NO: 2697)
1086D05	424	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHSPLSF (SEQ ID NO: 2461)
1086D06	425	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPPTAPLDL (SEQ ID NO: 2379)
1086D07	426	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPPTHLLTF (SEQ ID NO: 2365)
1086D08	427	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHSSLDF (SEQ ID NO: 2473)
1086D09	428	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPNHPMFP (SEQ ID NO: 2665)
1086D10	429	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPLSSLEF (SEQ ID NO: 2587)
1086D11	430	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAPLHP (SEQ ID NO: 2610)
1086D12	431	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRAHLRF (SEQ ID NO: 2469)
1086E02	432	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFYDPLHF (SEQ ID NO: 2621)
1086E03	433	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPFDALQS (SEQ ID NO: 2598)
1086E05	434	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRTPLTF (SEQ ID NO: 2567)
1086E07	435	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFAAHLSF (SEQ ID NO: 2398)
1086E08	436	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRAPLLF (SEQ ID NO: 2490)
1086E09	437	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPFSPLAP (SEQ ID NO: 2464)
1086E10	438	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRAPLDF (SEQ ID NO: 2367)
1086E12	439	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPPTAPLRF (SEQ ID NO: 2522)
1086F02	440	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSSPLRI (SEQ ID NO: 2714)
1086F05	441	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPTEPLQF (SEQ ID NO: 2540)
1086F08	442	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFSPDLSA (SEQ ID NO: 2643)
1086F09	443	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYNPIIF (SEQ ID NO: 2653)
1086F11	444	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHTPLLF (SEQ ID NO: 2489)
1086G03	445	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLDL (SEQ ID NO: 2513)
1086G04	446	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPFDFLLI (SEQ ID NO: 2454)
1086G05	447	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPPTDALRI (SEQ ID NO: 2537)
1086G06	448	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFAAPLTP (SEQ ID NO: 2407)
1086G07	449	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPEGPLLF (SEQ ID NO: 2448)
1086G09	450	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYAPLSF (SEQ ID NO: 2385)
1086G10	451	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAADLSF (SEQ ID NO: 2391)
1086H05	452	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYSPPLTH (SEQ ID NO: 2679)
1089A01	453	<u>138140</u> - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLFPHDPLI (SEQ ID NO: 2612)
1089A03	454	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPLTPLLI (SEQ ID NO: 2590)
1089A06	455	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHTPLHF (SEQ ID NO: 2485)

1089A07	456	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFTDALYF (SEQ ID NO: 2539)
1089A08	457	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYTPLF (SEQ ID NO: 2682)
1089A10	458	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHQPLTF (SEQ ID NO: 2436)
1089A11	459	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPRTYLD (SEQ ID NO: 2572)
1089B01	460	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSPHLS (SEQ ID NO: 2450)
1089B02	461	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHHSFDL (SEQ ID NO: 2147)
1089B03	462	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSTPLQP (SEQ ID NO: 2528)
1089B04	463	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHTPLF (SEQ ID NO: 2556)
1089B05	464	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLF (SEQ ID NO: 2712)
1089B06	465	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPMAPLSP (SEQ ID NO: 2596)
1089B07	466	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSGLDA (SEQ ID NO: 2374)
1089B08	467	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPAPLSP (SEQ ID NO: 2405)
1089B09	468	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKSPILF (SEQ ID NO: 2384)
1089B10	469	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSTPLFF (SEQ ID NO: 2571)
1089B11	470	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNSPLFP (SEQ ID NO: 2388)
1089C01	471	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
1089C02	472	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPKSPILF (SEQ ID NO: 2551)
1089C03	473	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYHPLLF (SEQ ID NO: 2532)
1089C05	474	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSALRF (SEQ ID NO: 2722)
1089C06	475	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSPYLSF (SEQ ID NO: 2701)
1089C07	476	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQAPLFD (SEQ ID NO: 2683)
1089C09	477	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHPFTF (SEQ ID NO: 2507)
1089D01	478	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHPAPLVL (SEQ ID NO: 2581)
1089D02	479	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHYGMDV (SEQ ID NO: 2133)
1089D03	480	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYHPLLF (SEQ ID NO: 2344)
1089D04	481	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSPPLSP (SEQ ID NO: 2717)
1089D05	482	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHPAPLFT (SEQ ID NO: 2546)
1089D07	483	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNDPLLI (SEQ ID NO: 2634)
1089D08	484	139 140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLFPHPAPLQ (SEQ ID NO: 2554)
1089D09	485	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSPHAFHE (SEQ ID NO: 2677)
1089D11	486	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPNHPLYP (SEQ ID NO: 2663)
1089E01	487	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPPLFP (SEQ ID NO: 2657)
1089E02	488	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQDPLHP (SEQ ID NO: 2346)
1089E03	489	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPDAPLFP (SEQ ID NO: 2423)
1089E04	490	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHPPLLI (SEQ ID NO: 2453)
1089E06	491	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSPPLF (SEQ ID NO: 2491)
1089E09	492	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSSPLTF (SEQ ID NO: 2718)
1089E10	493	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSTPLSF (SEQ ID NO: 2566)
1089E11	494	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPQPLWP (SEQ ID NO: 2578)
1089F01	495	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPSTPLF (SEQ ID NO: 2380)
1089F03	496	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPHPDPLLL (SEQ ID NO: 2580)
1089F04	497	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLFPYSPPLF (SEQ ID NO: 2670)

1089F05	498	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHSPLRI (SEQ ID NO: 2459)
1089F06	499	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRAPLLF (SEQ ID NO: 2490)
1089F08	500	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRTPPLTF (SEQ ID NO: 2567)
1089F09	501	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPLAPLSF (SEQ ID NO: 2555)
1089F10	502	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPNQPLSF (SEQ ID NO: 2667)
1089F11	503	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPLEPMHF (SEQ ID NO: 2565)
1089G01	504	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSAPLTF (SEQ ID NO: 2626)
1089G02	505	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSHPLLF (SEQ ID NO: 2687)
1089G03	506	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRTPLVF (SEQ ID NO: 2721)
1089G05	507	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPGSPLTF (SEQ ID NO: 2389)
1089G06	508	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPTAPLLF (SEQ ID NO: 2514)
1089G07	509	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSAPLDF (SEQ ID NO: 2597)
1089G08	510	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSHPLSF (SEQ ID NO: 2688)
1089G11	511	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSFPLLF (SEQ ID NO: 2671)
1089H10	512	†42141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSYGM DV (SEQ ID NO: 2135)
1090A02	513	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPAKPLLF (SEQ ID NO: 2416)
1090A03	514	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPNSLTSF (SEQ ID NO: 2678)
1090A04	515	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPDAPLTP (SEQ ID NO: 2426)
1090A05	516	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHEPLLI (SEQ ID NO: 2648)
1090A06	517	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPTYPPLSF (SEQ ID NO: 2600)
1090A07	518	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPTEPLVL (SEQ ID NO: 2479)
1090A08	519	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPTYPPLHF (SEQ ID NO: 2584)
1090B01	520	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHDPLTF (SEQ ID NO: 2627)
1090B03	521	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPQAPLTP (SEQ ID NO: 2705)
1090B04	522	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHAPLEA (SEQ ID NO: 2520)
1090B05	523	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPDHPLLF (SEQ ID NO: 2442)
1090B06	524	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRAPLSF (SEQ ID NO: 2496)
1090B08	525	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRGPLRF (SEQ ID NO: 2542)
1090B11	526	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPFTPLTF (SEQ ID NO: 2474)
1090B12	527	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPQHPPLSP (SEQ ID NO: 2452)
1090C01	528	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSAPIVF (SEQ ID NO: 2591)
1090C02	529	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPQAPLTF (SEQ ID NO: 2702)
1090C03	530	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRAPLRF (SEQ ID NO: 2493)
1090C05	531	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRTPPLTF (SEQ ID NO: 2567)
1090C06	532	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHAPLDF (SEQ ID NO: 2538)
1090C07	533	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHAGFDS (SEQ ID NO: 2498)
1090C08	534	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSPLSF (SEQ ID NO: 2676)
1090C10	535	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPGRPLTF (SEQ ID NO: 2358)
1090D02	536	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPAEHLF (SEQ ID NO: 2408)
1090D03	537	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPTAPLHP (SEQ ID NO: 2351)
1090D04	538	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHEPLTA (SEQ ID NO: 2654)
1090D05	539	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHAPLFE (SEQ ID NO: 2529)

1090D06	540	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPLDF (SEQ ID NO: 2367)
1090D07	541	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPFGTLRF (SEQ ID NO: 2462)
1090D08	542	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSSPLVF (SEQ ID NO: 2723)
1090D09	543	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPDPPLAF (SEQ ID NO: 2505)
1090D12	544	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTSPLSF (SEQ ID NO: 2579)
1090E04	545	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPLLL (SEQ ID NO: 2552)
1090E05	546	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPISF (SEQ ID NO: 2588)
1090E06	547	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQGPLSF (SEQ ID NO: 2443)
1090E07	548	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPGSPLHP (SEQ ID NO: 2484)
1090E09	549	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFSDPLSF (SEQ ID NO: 2647)
1090E11	550	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHDGLAP (SEQ ID NO: 2700)
1090E12	551	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTSPLTF (SEQ ID NO: 2582)
1090F01	552	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNGPLHP (SEQ ID NO: 2649)
1090F02	553	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLSF (SEQ ID NO: 2696)
1090F03	554	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTAPLSF (SEQ ID NO: 2526)
1090F04	555	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPFPLQF (SEQ ID NO: 2460)
1090F05	556	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPLDPLHF (SEQ ID NO: 2359)
1090F06	557	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSEPLQL (SEQ ID NO: 2666)
1090F07	558	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPFAPLRF (SEQ ID NO: 2451)
1090F08	559	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPLHPLIF (SEQ ID NO: 2570)
1090F09	560	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1090F10	561	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRDPLRI (SEQ ID NO: 2527)
1090F11	562	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSNPLTF (SEQ ID NO: 2698)
1090G01	563	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTAPLEI (SEQ ID NO: 2347)
1090G02	564	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRDPLQF (SEQ ID NO: 2395)
1090G04	565	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHEPLAF (SEQ ID NO: 2633)
1090G05	566	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPLAF (SEQ ID NO: 2472)
1090G06	567	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYSPLAF (SEQ ID NO: 2656)
1090G07	568	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHTPPLDS (SEQ ID NO: 2480)
1090G08	569	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHTPPLTF (SEQ ID NO: 2492)
1090G09	570	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSEPLRI (SEQ ID NO: 2356)
1090G10	571	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTAPLDF (SEQ ID NO: 2343)
1090G12	572	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNRGLDL (SEQ ID NO: 2669)
1091A02	573	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYDPLFM (SEQ ID NO: 2724)
1091A03	574	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPLYP (SEQ ID NO: 2592)
1091A06	575	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSAPLAF (SEQ ID NO: 2594)
1091A11	576	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPITF (SEQ ID NO: 2441)
1091B01	577	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYPLFF (SEQ ID NO: 2585)
1091B02	578	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYAPLDF (SEQ ID NO: 2361)
1091B04	579	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRDPLQF (SEQ ID NO: 2395)
1091B05	580	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLEL (SEQ ID NO: 2475)
1091B07	581	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSAPLTF (SEQ ID NO: 2626)

1091B10	582	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFTAPLAF (SEQ ID NO: 2342)
1091B11	583	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPLDF (SEQ ID NO: 2444)
1091B12	584	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPLTF (SEQ ID NO: 2690)
1091C02	585	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAHPLVI (SEQ ID NO: 2414)
1091C03	586	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFQAAPLYP (SEQ ID NO: 2378)
1091C04	587	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFTAPLTF (SEQ ID NO: 2531)
1091C05	588	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFTTPLHF (SEQ ID NO: 2583)
1091C06	589	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1091C09	590	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHPLSF (SEQ ID NO: 2415)
1091C11	591	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFYHSDI (SEQ ID NO: 2650)
1091C12	592	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFYATLSF (SEQ ID NO: 2618)
1091D01	593	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNSPLAP (SEQ ID NO: 2672)
1091D02	594	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYSPLP (SEQ ID NO: 2673)
1091D04	595	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQPLSF (SEQ ID NO: 2443)
1091D05	596	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHDPLAP (SEQ ID NO: 2606)
1091D06	597	†38140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLFPHSPLL (SEQ ID NO: 2456)
1091D07	598	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNGALRF (SEQ ID NO: 2645)
1091D09	599	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYSPLP (SEQ ID NO: 2719)
1091E01	600	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPDAPLHP (SEQ ID NO: 2425)
1091E02	601	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLFP (SEQ ID NO: 2689)
1091E03	602	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPLWP (SEQ ID NO: 2352)
1091E04	603	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPKSPPLAF (SEQ ID NO: 2547)
1091E06	604	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSSPLHP (SEQ ID NO: 2576)
1091E07	605	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNHPLTF (SEQ ID NO: 2661)
1091E08	606	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAPLDS (SEQ ID NO: 2607)
1091E09	607	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYAPLDF (SEQ ID NO: 2361)
1091E10	608	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSSPLEF (SEQ ID NO: 2711)
1091F01	609	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPLFF (SEQ ID NO: 2486)
1091F03	610	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPLAPLHP (SEQ ID NO: 2599)
1091F05	611	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPLAPLHP (SEQ ID NO: 2553)
1091F06	612	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHDPLGF (SEQ ID NO: 2353)
1091F07	613	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYGMDV (SEQ ID NO: 2133)
1091F08	614	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQSPPLF (SEQ ID NO: 2458)
1091F09	615	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHLSF (SEQ ID NO: 2354)
1091F10	616	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPLDF (SEQ ID NO: 2444)
1091F11	617	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPLSP (SEQ ID NO: 2549)
1091F12	618	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYGMDV (SEQ ID NO: 2133)
1091G01	619	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAALYP (SEQ ID NO: 2386)
1091G03	620	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNDPLFG (SEQ ID NO: 2355)
1091G04	621	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPLSP (SEQ ID NO: 2478)
1091G05	622	†39141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	ARDLLLLFPAAPLWP (SEQ ID NO: 2397)
1091G06	623	†38140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLFPNDPLR (SEQ ID NO: 2637)

1091G07	624	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTAPLDP (SEQ ID NO: 2345)
1091G09	625	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTAPLFP (SEQ ID NO: 2349)
1091G10	626	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFSDPLVF (SEQ ID NO: 2660)
1091G11	627	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFGSPLTF (SEQ ID NO: 2389)
1091G12	628	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYSHLEF (SEQ ID NO: 2655)
1104A01	629	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFQSPPLHP (SEQ ID NO: 2455)
1104A07	630	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFQAPLFP (SEQ ID NO: 2689)
1104A08	631	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYAPLTF (SEQ ID NO: 2617)
1104A09	632	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFQNPPLHP (SEQ ID NO: 2506)
1104A10	633	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFHEPLCF (SEQ ID NO: 2636)
1104A11	634	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPMAPLRF (SEQ ID NO: 2593)
1104A12	635	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRSPLSF (SEQ ID NO: 2557)
1104B02	636	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFSPALYP (SEQ ID NO: 2387)
1104B04	637	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRDP LQF (SEQ ID NO: 2395)
1104B09	638	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPTAPLTF (SEQ ID NO: 2531)
1104B11	639	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYSPLYP (SEQ ID NO: 2710)
1104C01	640	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPASPLIF (SEQ ID NO: 2417)
1104C04	641	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRHP LLF (SEQ ID NO: 2543)
1104C05	642	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLE (SEQ ID NO: 2524)
1104C06	643	<u>138140</u> - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SRDLLLLFPHAPLHP (SEQ ID NO: 2370)
1104C07	644	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHPLIF (SEQ ID NO: 2399)
1104C09	645	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFHEPLIF (SEQ ID NO: 2644)
1104C11	646	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNHAFDL (SEQ ID NO: 2652)
1104D01	647	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHTILYP (SEQ ID NO: 2497)
1104D02	648	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPDWPLYP (SEQ ID NO: 2483)
1104D03	649	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLFL (SEQ ID NO: 2511)
1104D04	650	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLHP (SEQ ID NO: 2691)
1104D07	651	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPMDP (SEQ ID NO: 2595)
1104D08	652	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRAPLTF (SEQ ID NO: 2500)
1104D09	653	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRA TLEF (SEQ ID NO: 2502)
1104E01	654	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSPLFP (SEQ ID NO: 2447)
1104E02	655	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNDPLVL (SEQ ID NO: 2641)
1104E03	656	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHDPLYI (SEQ ID NO: 2463)
1104E05	657	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYAPLSF (SEQ ID NO: 2385)
1104E11	658	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPASPLNP (SEQ ID NO: 2364)
1104E12	659	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHDPLSP (SEQ ID NO: 2616)
1104F02	660	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRDPLRF (SEQ ID NO: 2360)
1104F03	661	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPGDPLDF (SEQ ID NO: 2481)
1104F04	662	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHGPLTF (SEQ ID NO: 2402)
1104F05	663	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLSP (SEQ ID NO: 2573)
1104F06	664	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSSPLIL (SEQ ID NO: 2465)
1104F07	665	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	

1104F10	666	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNPLSP (SEQ ID NO: 2362)
1104F11	667	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPQDPLVF (SEQ ID NO: 2708)
1104F12	668	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPKAPLVF (SEQ ID NO: 2544)
1104G04	669	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLRF (SEQ ID NO: 2559)
1104G05	670	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAP (SEQ ID NO: 2476)
1104G09	671	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPTAPLNF (SEQ ID NO: 2518)
1104G11	672	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRHLLLLFQPLSF (SEQ ID NO: 2482)
1105A02	673	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHLP (SEQ ID NO: 2494)
1105A03	674	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1105A04	675	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPQAPLAP (SEQ ID NO: 2487)
1105A08	676	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPRPLSF (SEQ ID NO: 2557)
1105A09	677	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1105A11	678	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHHSFDL (SEQ ID NO: 2692)
1105B04	679	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYPLHP (SEQ ID NO: 2658)
1105B05	680	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYPLSF (SEQ ID NO: 2676)
1105B07	681	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1105B08	682	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1105B10	683	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPASPLNP (SEQ ID NO: 2364)
1105B11	684	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHPLSP (SEQ ID NO: 2651)
1105B12	685	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPLDPLII (SEQ ID NO: 2560)
1105C02	686	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLAF (SEQ ID NO: 2472)
1105C03	687	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPSSPLSF (SEQ ID NO: 2715)
1105C05	688	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYGMDV (SEQ ID NO: 2133)
1105C06	689	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLDF (SEQ ID NO: 2367)
1105C08	690	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPRSP (SEQ ID NO: 2562)
1105D04	691	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPQHGFD (SEQ ID NO: 2446)
1105D06	692	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPRDPLRF (SEQ ID NO: 2360)
1105D08	693	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPRDPLSF (SEQ ID NO: 2368)
1105D09	694	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYAPLAF (SEQ ID NO: 2608)
1105D10	695	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHAAFDV (SEQ ID NO: 2619)
1105D11	696	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHPLFP (SEQ ID NO: 2640)
1105E01	697	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPRSALTF (SEQ ID NO: 2519)
1105E06	699	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHHSFDS (SEQ ID NO: 2422)
1105E11	700	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYGMDV (SEQ ID NO: 2133)
1105F03	701	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNPLHP (SEQ ID NO: 2675)
1105F06	702	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHPLDS (SEQ ID NO: 2409)
1105F07	703	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPQAPLHP (SEQ ID NO: 2691)
1105F09	704	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFSPWPLTF (SEQ ID NO: 2340)
1105F12	705	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1105G03	706	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPTPLVF (SEQ ID NO: 2604)
1105G08	707	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHAPLHP (SEQ ID NO: 2370)
										SRDLLLLFPKHPLVF (SEQ ID NO: 2366)

1105G09	708	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPASPLNP (SEQ ID NO: 2364)
1105G10	709	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHHSFDA (SEQ ID NO: 2419)
1105G11	710	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHDPLLF (SEQ ID NO: 2614)
1107A01	711	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRHPLVF (SEQ ID NO: 2545)
1107A03	712	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRAPLYP (SEQ ID NO: 2501)
1107A06	713	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLDP (SEQ ID NO: 2369)
1107A07	714	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAPLSP (SEQ ID NO: 2371)
1107A09	715	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLSP (SEQ ID NO: 2699)
1107A12	716	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLSF (SEQ ID NO: 2564)
1107B02	717	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLFP (SEQ ID NO: 2533)
1107B04	718	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPASPLTF (SEQ ID NO: 2420)
1107B05	719	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYGMDV (SEQ ID NO: 2133)
1107C01	720	<u>†37139</u> - 247	137 - 247	161 - 171	187 - 193	226 - 236	1 - 121	24 - 33	48 - 64	97 - 110	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1107C02	721	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYGMYY (SEQ ID NO: 2504)
1107C04	722	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLHP (SEQ ID NO: 2357)
1107C06	723	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLAP (SEQ ID NO: 2510)
1107C08	724	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLEP (SEQ ID NO: 2681)
1107C10	725	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAFDL (SEQ ID NO: 2674)
1107D01	726	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYAPLDF (SEQ ID NO: 2361)
1107D04	727	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAPLSF (SEQ ID NO: 2625)
1107D07	728	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHSFDV (SEQ ID NO: 2693)
1107D12	729	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDT (SEQ ID NO: 2424)
1107E01	730	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPMGLDL (SEQ ID NO: 2499)
1107E05	731	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRAPLDF (SEQ ID NO: 2367)
1107E07	732	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPKAPLTF (SEQ ID NO: 2551)
1107E09	733	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPPSAPLSP (SEQ ID NO: 2623)
1107F01	734	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLAP (SEQ ID NO: 2510)
1107F05	735	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSAPLAP (SEQ ID NO: 2394)
1107F09	736	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRTPLLF (SEQ ID NO: 2373)
1107F10	737	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAPLSP (SEQ ID NO: 2371)
1107G01	738	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPSAPLYP (SEQ ID NO: 2387)
1107G05	739	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1107H02	740	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRAPLSF (SEQ ID NO: 2496)
1107H06	741	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLEM (SEQ ID NO: 2536)
1107H09	742	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHAPLAP (SEQ ID NO: 2510)
1107H10	743	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1108A12	744	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPRDPLLF (SEQ ID NO: 2515)
1108B03	745	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPLSPLVP (SEQ ID NO: 2396)
1108B04	746	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHDPLGF (SEQ ID NO: 2353)
1108C09	747	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSLLF (SEQ ID NO: 2429)
1108C11	748	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPASPLNP (SEQ ID NO: 2364)
1108D10	749	<u>†39141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	

1108D11	750	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPASPLNP (SEQ ID NO: 2364)
1108D12	751	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSAPLNP (SEQ ID NO: 2709)
1108E01	752	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHHSFDL (SEQ ID NO: 2147)
1108E03	753	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPKHPLRF (SEQ ID NO: 2393)
1108E05	754	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHAPLFP (SEQ ID NO: 2533)
1108E07	755	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHAPLDP (SEQ ID NO: 2369)
1108E08	756	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHYPLLF (SEQ ID NO: 2344)
1108E09	757	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSAPLSP (SEQ ID NO: 2623)
1108E10	758	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRDPLDL (SEQ ID NO: 2509)
1108E11	759	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRDPLEF (SEQ ID NO: 2516)
1108F10	760	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAPLSP (SEQ ID NO: 2371)
1108F12	761	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHYPFDA (SEQ ID NO: 2508)
1108G01	762	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRDPLRF (SEQ ID NO: 2360)
1108G02	763	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPDAPLAP (SEQ ID NO: 2381)
1108G07	764	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRAPLAP (SEQ ID NO: 2476)
1108G10	765	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHHSLLF (SEQ ID NO: 2429)
1108G11	766	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHPLTF (SEQ ID NO: 2377)
1108G12	767	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHPLTF (SEQ ID NO: 2377)
1108H01	768	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRDPLHF (SEQ ID NO: 2512)
1108H02	769	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPNAPLNP (SEQ ID NO: 2615)
1108H06	770	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHHSFDL (SEQ ID NO: 2147)
1108H08	771	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPASPLNP (SEQ ID NO: 2364)
1111A06	772	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLHP (SEQ ID NO: 2691)
1111B12	773	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHHSFDL (SEQ ID NO: 2147)
1111C01	774	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQHGLDL (SEQ ID NO: 2449)
1111D06	775	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRDPLLF (SEQ ID NO: 2515)
1111E04	776	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLHP (SEQ ID NO: 2691)
1111E10	777	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1111E11	778	<u>139</u> 141 - 250	139 - 250	163 - 173	189 - 195	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHHSFDL (SEQ ID NO: 2150)
1111E12	779	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPRAPLYP (SEQ ID NO: 2501)
1111F07	780	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPKAPLDF (SEQ ID NO: 2534)
1111G02	781	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQHGFD (SEQ ID NO: 2703)
1111H10	782	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPSAPLWP (SEQ ID NO: 2352)
1113A04	783	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFQEPAPLAP (SEQ ID NO: 2434)
1113A12	784	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHPLP (SEQ ID NO: 2411)
1113B06	785	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHHSFDL (SEQ ID NO: 2406)
1113C06	786	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHYPLLF (SEQ ID NO: 2344)
1113G04	787	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLPHYSLLL (SEQ ID NO: 2517)
1113G05	788	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHPLQF (SEQ ID NO: 2413)
1113G10	789	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1113G11	790	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1113H06	791	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)

1113H07	792	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1113H09	793	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYTLF (SEQ ID NO: 2525)
1114C04	794	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHGFDA (SEQ ID NO: 2406)
1114C12	795	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLHP (SEQ ID NO: 2691)
1114D04	796	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYGMDV (SEQ ID NO: 2133)
1114D06	797	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1114D10	798	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYSVL (SEQ ID NO: 2521)
1114E01	799	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQEP LSP (SEQ ID NO: 2435)
1114E02	800	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQESFSL (SEQ ID NO: 2437)
1114E03	801	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPKAPLTF (SEQ ID NO: 2382)
1114E11	802	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHDSFFL (SEQ ID NO: 2383)
1114H01	803	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1114H06	804	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHALDV (SEQ ID NO: 2404)
1114H09	805	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1115A02	806	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPDHSFDL (SEQ ID NO: 2684)
1115A07	807	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1115B10	808	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1115C05	809	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPAPLYP (SEQ ID NO: 2501)
1115C06	810	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2150)
1115C08	811	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1115C12	812	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDT (SEQ ID NO: 2424)
1115D07	813	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1115E09	814	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHRFDL (SEQ ID NO: 2418)
1115F06	815	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYGMDV (SEQ ID NO: 2685)
1115F07	816	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2686)
1115F12	817	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2150)
1115G04	818	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHRFDL (SEQ ID NO: 2418)
1115G05	819	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1115G08	820	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHDSFDL (SEQ ID NO: 2631)
1115H04	821	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHANLSP (SEQ ID NO: 2503)
1115H07	822	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1115H09	823	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHRFDL (SEQ ID NO: 2147)
1116A07	824	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPYEPLRF (SEQ ID NO: 2642)
1116B01	825	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1116B12	826	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1116C06	827	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1116D07	828	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHRFDL (SEQ ID NO: 2147)
1116E02	829	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2147)
1116E04	830	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHRFDL (SEQ ID NO: 2418)
1116F02	831	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHHSFDL (SEQ ID NO: 2150)
1116F11	832	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPHYPLLF (SEQ ID NO: 2344)
1116G05	833	<u>139</u> 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLLLFPQAPLSP (SEQ ID NO: 2699)

1001C09	834	143142 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYIDNYMDV (SEQ ID NO: 2154)
1006D07	835	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
1007B03	836	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYIDNYMDV (SEQ ID NO: 2154)
1007F11	837	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DGIDILLVPAALMDV (SEQ ID NO: 2160)
1007H08	838	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYYGMDV (SEQ ID NO: 2129)
1008A09	839	146 - 256	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 66	99 - 119	DREAYDILTGYLYYYMDV (SEQ ID NO: 2172)
1008B01	840	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008C02	841	145 - 255	145 - 255	167 - 180	196 - 202	235 - 244	1 - 129	26 - 37	52 - 67	100 - 118	HVRDYDILTGYRGHYFDY (SEQ ID NO: 2167)
1008C03	842	143142 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 65	98 - 116	EGSYDILTGYVGVGRMDV (SEQ ID NO: 2171)
1008C12	843	146 - 256	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 68	101 - 119	FNPTYDILTGYIGGYFQH (SEQ ID NO: 2155)
1012A06	844	145147 - 254	145 - 254	169 - 179	195 - 201	234 - 243	1 - 129	26 - 37	52 - 67	100 - 118	GRWDYDLLTGEHLGYFDY (SEQ ID NO: 2162)
1016E05	845	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016F02	846	135 - 245	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1016F04	847	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016H07	848	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	GYHDPLTSYNNWFDP (SEQ ID NO: 2163)
1018C02	849	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018C10	850	143142 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYIDNYMDV (SEQ ID NO: 2154)
1018D07	851	143142 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYIDNYMDV (SEQ ID NO: 2154)
1018H08	852	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018H09	853	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1021B05	854	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYIGNGAFDI (SEQ ID NO: 2158)
1022E02	855	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2157)
1026E03	856	141143 - 251	141 - 251	165 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	TDYDILTGYPMGYFDP (SEQ ID NO: 2173)
1027A07	857	144145 - 255	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	GGEYDILTGYFGLGVYDY (SEQ ID NO: 2170)
1028A06	858	142 - 253	142 - 253	164 - 176	192 - 198	231 - 242	1 - 126	26 - 35	50 - 66	99 - 115	GGDYDILTGLYYGMDV (SEQ ID NO: 2156)
1029D07	859	141 - 250	141 - 250	163 - 176	192 - 198	231 - 239	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1029F11	860	143 - 253	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYIDNYMDV (SEQ ID NO: 2154)
1031C03	861	137138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031C07	862	147148 - 258	147 - 258	170 - 183	199 - 205	238 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPRWYDALTGDSYHSAMDV (SEQ ID NO: 2169)
1031F09	863	143145 - 255	143 - 255	167 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	DEGRDLLTGYWPNFFDS (SEQ ID NO: 2168)
1031G08	864	147148 - 259	147 - 259	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWDALTGHSYHSAMDV (SEQ ID NO: 2159)
1031G10	865	147148 - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWDALTGDSYHSAMDV (SEQ ID NO: 2165)
1031G11	866	143145 - 255	143 - 255	167 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	DEGRDLLTGYWPNFFDS (SEQ ID NO: 2168)
1037E07	867	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DGIDILLVPAALMDV (SEQ ID NO: 2160)
1037E12	868	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DGIDILLVPAALMDV (SEQ ID NO: 2160)
1050A07	869	145146 - 257	145 - 257	168 - 181	197 - 203	236 - 246	1 - 129	26 - 40	55 - 71	104 - 118	QDNPLTGYKLGFDY (SEQ ID NO: 2164)
1061D02	870	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYYGMDV (SEQ ID NO: 2129)
1061E07	871	141 - 251	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1061H01	872	146 - 256	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 68	101 - 119	FNPTYDILTGYIGGYFQH (SEQ ID NO: 2155)
1001A03	873	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERHYDILTGYQTGYGMDV (SEQ ID NO: 2784)
1001A07	874	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1001A08	875	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)

1001A10	876	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1001A12	877	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1001B02	878	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	DRETKVGYGMDV (SEQ ID NO: 2945)
1001B07	879	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1001C06	880	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
1001C08	881	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
1001C12	882	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1001D08	883	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 65	98 - 113	DSYDILTGYYGYFDY (SEQ ID NO: 2745)
1001D12	884	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1001E05	885	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
1001E07	886	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1001G09	887	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1001H05	888	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERHYDILTGYYQTYGMDV (SEQ ID NO: 2784)
1001H08	889	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1003A01	890	140 141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1003A06	891	140 141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1003A07	892	142 141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSYGYMDV (SEQ ID NO: 2135)
1003A10	893	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1003B03	894	140 141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1003B04	895	138 140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	25 - 34	49 - 65	98 - 111	RYGDPFYYYMNV (SEQ ID NO: 2755)
1003B09	896	142 141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSYGYMDV (SEQ ID NO: 2135)
1003C01	897	140 142 - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2174)
1003C02	898	141 142 - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPACFCQI (SEQ ID NO: 2854)
1003C03	899	141 142 - 250	141 - 250	164 - 174	190 - 196	229 - 239	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPACFCQI (SEQ ID NO: 2854)
1003C12	900	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYYGGYFDY (SEQ ID NO: 2179)
1003D04	901	139 140 - 250	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1003E05	902	141 142 - 253	141 - 253	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPACFCQI (SEQ ID NO: 2854)
1003F01	903	140 141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1003F02	904	139 140 - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1003G01	905	143 145 - 254	143 - 254	168 - 179	195 - 201	234 - 243	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYYMGSAFDQ (SEQ ID NO: 2800)
1003G05	906	143 144 - 255	143 - 255	166 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	GSYDILTGYYTGSPLDY (SEQ ID NO: 2766)
1003G06	907	145 146 - 256	145 - 256	168 - 181	197 - 203	236 - 245	1 - 129	26 - 35	50 - 66	99 - 118	DRGNYDILTGYYFHHGV (SEQ ID NO: 2914)
1003G11	908	144 143 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DAQSYDILTGYSYAFDI (SEQ ID NO: 2183)
1003H02	909	140 142 - 253	140 - 253	164 - 176	192 - 198	233 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
1003H05	910	140 141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1003H08	911	142 141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSYGYMDV (SEQ ID NO: 2135)
1003A01	912	141 140 - 249	141 - 249	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
1003A02	913	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	EGRDILTGYYGYGLDY (SEQ ID NO: 2893)
1003B01	914	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
1003B09	915	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 65	98 - 110	TYDILTGRFFDI (SEQ ID NO: 2866)
1003C01	916	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
1003D02	917	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	DLRYDILTGYPHDAFDI (SEQ ID NO: 2890)

1005D03	918	142 - 249	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GAYYDILTGYYPYGMDV (SEQ ID NO: 2860)
1005E01	919	142 - 249	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GTYDILTGYYFHYGMDV (SEQ ID NO: 2774)
1005E08	920	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYYWFDL (SEQ ID NO: 2166)
1005F01	921	140 142 - 248	140 - 248	164 - 174	190 - 196	229 - 238	1 - 124	26 - 35	50 - 66	99 - 113	DQHDILTGYYGMDV (SEQ ID NO: 2921)
1005F02	922	144 - 251	144 - 251	167 - 177	193 - 199	232 - 240	1 - 128	26 - 35	50 - 66	99 - 117	VSPSYDILTGYYLPHAFDV (SEQ ID NO: 2849)
1005F04	923	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 65	98 - 110	TYDYDILTGRFFDI (SEQ ID NO: 2866)
1005F08	924	140 139 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	PSYDILTGYYLYFDY (SEQ ID NO: 2850)
1005G01	925	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	DLRYDILTGYYHDAFDI (SEQ ID NO: 2890)
1005G08	926	142 - 249	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GAYYDILTGYYPYGMDV (SEQ ID NO: 2860)
1005H02	927	140 139 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	GQYYDILTGYNWFDP (SEQ ID NO: 2857)
1006B01	928	139 138 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLFPHYGMDV (SEQ ID NO: 2133)
1006C09	929	143 - 253	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GGYSSGWLRCGPYNWFDP (SEQ ID NO: 2967)
1006D09	930	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYYIPLRDY (SEQ ID NO: 2792)
1006E01	931	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 68	101 - 116	NLFDVWTLPPYYMDV (SEQ ID NO: 2965)
1006E07	932	143 - 250	143 - 250	166 - 176	192 - 198	231 - 239	1 - 127	26 - 35	50 - 66	99 - 116	ADYDILTGYSPLTYGMDV (SEQ ID NO: 2762)
1006F01	933	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 68	101 - 113	MYDYDILTGHNFY (SEQ ID NO: 2879)
1006F02	934	142 - 253	142 - 253	164 - 176	192 - 198	231 - 242	1 - 126	26 - 35	50 - 66	99 - 115	VSRDILTGNYYYGMDV (SEQ ID NO: 2817)
1006F07	935	143 - 253	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GGYSSGWLRCGPYNWFDP (SEQ ID NO: 2967)
1006G01	936	146 - 253	146 - 253	169 - 179	195 - 201	234 - 242	1 - 130	26 - 35	50 - 68	101 - 119	AGGYDILTGRDYYGMDV (SEQ ID NO: 2877)
1006G04	937	142 131 - 239	132 - 239	153 - 163	179 - 185	218 - 228	1 - 116	26 - 35	50 - 66	99 - 105	RRYALDY (SEQ ID NO: 2920)
1006H01	938	146 145 - 253	146 - 253	167 - 177	193 - 199	232 - 242	1 - 130	26 - 35	50 - 65	98 - 119	DRGSYDILTGYYTPPHYYGMDV (SEQ ID NO: 2761)
1006H02	939	143 - 253	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GGYSSGWLRCGPYNWFDP (SEQ ID NO: 2967)
1007A01	940	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1007A08	941	139 - 249	139 - 249	161 - 174	190 - 196	229 - 238	1 - 123	26 - 35	50 - 66	99 - 114	SHYDILTGLNYYWFDY (SEQ ID NO: 2746)
1007A11	942	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ENYDPLTGYYGAFDI (SEQ ID NO: 2772)
1007A12	943	144 143 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 68	101 - 117	GIYDILTGYYHWDGAFDI (SEQ ID NO: 2892)
1007B04	944	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1007C04	945	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1007C08	946	142 141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 65	98 - 115	IRLYCYSLTGYYPYGMDD (SEQ ID NO: 2810)
1007C12	947	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	TNYDILTGYYQGVDY (SEQ ID NO: 2782)
1007D07	948	140 139 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	GQYYDILTGYNWFDP (SEQ ID NO: 2857)
1007D08	949	144 143 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 68	101 - 117	GIYDILTGYYHWDGAFDI (SEQ ID NO: 2872)
1007E03	950	144 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1007E10	951	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	DFYDILTGYPGLGMDV (SEQ ID NO: 2741)
1007E11	952	144 143 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DLPPYDILTGYSLTSGMDV (SEQ ID NO: 2923)
1007F06	953	144 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1007F08	954	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	GRRYDILTGYYHHGMDV (SEQ ID NO: 2811)
1007G07	955	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYYWFDL (SEQ ID NO: 2166)
1007G09	956	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	DSGGDILTGYYMPYFDY (SEQ ID NO: 2847)
1007G10	957	142 141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 65	98 - 115	VGLYYDILTGYYPSGMDV (SEQ ID NO: 2805)
1007H07	958	147 - 257	147 - 257	169 - 182	198 - 204	237 - 246	1 - 131	26 - 35	50 - 68	101 - 120	SOAHYDILTGYYLWSYGMDV (SEQ ID NO: 2875)
1007H11	959	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ESYDILTGYRHYGMDL (SEQ ID NO: 2891)

1008A02	960	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008A05	961	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008A06	962	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008A07	963	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008A12	964	140 - 250	142 - 249	162 - 175	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DREYDILTGYYLHAFDM (SEQ ID NO: 2960)
1008B02	965	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ENYDPLTGYYGAFDI (SEQ ID NO: 2772)
1008B04	966	141 - 251	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008B05	967	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
1008B06	968	141 - 251	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	DHYDILTGYYGMDV (SEQ ID NO: 2760)
1008B07	969	140 - 247	140 - 247	163 - 173	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008B10	970	141 - 251	141 - 251	163 - 173	189 - 195	228 - 236	1 - 124	26 - 35	48 - 64	97 - 113	GRYDILTGYYKGPLDY (SEQ ID NO: 2902)
1008B11	971	144 - 254	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	AYYDNLTGFLPYGMDV (SEQ ID NO: 2947)
1008C06	972	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 117	EGYDILTGYYFHYGMDV (SEQ ID NO: 2753)
1008C08	973	149 - 259	149 - 259	171 - 183	199 - 205	238 - 248	1 - 133	26 - 35	50 - 66	99 - 122	GPRGPPYDILTGYYLSLDAFDI (SEQ ID NO: 2729)
1008C09	974	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	EYYDILTGYPYGMVDV (SEQ ID NO: 2973)
1008D01	975	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008D02	976	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008D03	977	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRYDILTRSFLAGPLDN (SEQ ID NO: 2751)
1008D04	978	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008D05	979	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008D06	980	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008D07	981	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008D08	982	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DRGYDILTGYYRGHGMVDV (SEQ ID NO: 2837)
1008D12	983	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DLPYYDILTGYSLSLTSMDV (SEQ ID NO: 2923)
1008E01	984	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 117	EEGYDILTGYPGYFDY (SEQ ID NO: 2974)
1008E02	985	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008E03	986	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008E04	987	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008E08	988	141 - 252	141 - 252	163 - 175	191 - 197	230 - 241	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGLNYWYFDL (SEQ ID NO: 2166)
1008E09	989	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	ERADYDILTGYYFYDMDV (SEQ ID NO: 2833)
1008E12	990	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	52 - 67	100 - 114	FRYDILTSYYGMDV (SEQ ID NO: 2734)
1008F03	991	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008F06	992	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008F07	993	143 - 253	143 - 253	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 65	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008F08	994	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	GRYDILTGYYHHGMVDV (SEQ ID NO: 2811)
1008F09	995	133 - 243	133 - 243	155 - 168	184 - 190	223 - 232	1 - 117	26 - 35	50 - 65	99 - 116	GHYDILTGDDYYGMDV (SEQ ID NO: 2844)
1008F10	996	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	98 - 106	HDILTGFDY (SEQ ID NO: 2904)
1008F11	997	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 113	SGYDILTGYYGMDV (SEQ ID NO: 2934)
1008G02	998	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 68	101 - 117	APYDILTGYSFDFDI (SEQ ID NO: 2968)
1008G03	999	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1008G04	1000	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	99 - 113	GDYDPLTGYSFDFDI (SEQ ID NO: 2941)
1008G05	1001	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	98 - 116	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
										99 - 117	DGYDILTGYYVGVGRMDV (SEQ ID NO: 2899)

1008G11	1002	136 - 246	136 - 246	158 - 171	187 - 193	226 - 235	1 - 120	26 - 35	50 - 66	99 - 109	AYYDILTGLDY (SEQ ID NO: 2966)
1008G12	1003	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DQQYDILTYGYIHYGMDV (SEQ ID NO: 2964)
1008H02	1004	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	DQYDILLMDHNYMMDV (SEQ ID NO: 2918)
1008H03	1005	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSDGFDI (SEQ ID NO: 2153)
1008H06	1006	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	EGSYDILTYGYVGVGRMDV (SEQ ID NO: 2171)
1008H09	1007	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DQQYDILTYGYIHYGMDV (SEQ ID NO: 2964)
1008H11	1008	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	TKYDILTYGYYYMMDV (SEQ ID NO: 2856)
1012B03	1009	140141 - 249	140 - 249	163 - 175	191 - 197	230 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012B06	1010	140141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012B10	1011	140141 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012C03	1012	142143 - 255	142 - 255	165 - 178	194 - 200	233 - 244	1 - 126	26 - 35	50 - 66	99 - 113	TDRFGAKDVTSRWGMDV (SEQ ID NO: 2814)
1012C06	1013	140141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012C09	1014	140142 - 250	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012D12	1015	145146 - 256	145 - 256	168 - 180	196 - 202	235 - 245	1 - 129	26 - 35	50 - 66	99 - 118	DRGNYDILTYGYFHHGV (SEQ ID NO: 2914)
1012E07	1016	140142 - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012E08	1017	139140 - 250	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1012E09	1018	140141 - 247	140 - 247	163 - 173	189 - 195	228 - 236	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012F05	1019	140141 - 249	140 - 249	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012F12	1020	140142 - 251	140 - 251	164 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012G03	1021	140142 - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012G05	1022	139141 - 250	139 - 250	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1012G10	1023	139140 - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1012H09	1024	140141 - 249	140 - 249	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1013A10	1025	147148 - 259	147 - 259	170 - 182	198 - 204	237 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1013A12	1026	147149 - 256	147 - 256	171 - 181	197 - 203	236 - 245	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1013B04	1027	147149 - 256	147 - 256	172 - 182	198 - 204	237 - 245	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGHSYHSAMDV (SEQ ID NO: 2165)
1013B09	1028	147149 - 257	147 - 257	171 - 181	197 - 203	236 - 246	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1013C02	1029	147148 - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGDSYRSAMDV (SEQ ID NO: 2818)
1013C04	1030	137139 - 249	137 - 249	161 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013D02	1031	137138 - 248	137 - 248	160 - 173	189 - 195	228 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013D03	1032	147148 - 259	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGDSYHSAMDV (SEQ ID NO: 2165)
1013D10	1033	145146 - 257	145 - 257	168 - 181	197 - 203	236 - 246	1 - 129	26 - 35	50 - 66	99 - 118	GLRHVTLFGTGRGHFYMDV (SEQ ID NO: 2789)
1013E02	1034	147148 - 259	147 - 259	170 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWRYYHYMDV (SEQ ID NO: 2809)
1013E05	1035	137139 - 249	137 - 249	162 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013E09	1036	147148 - 260	147 - 260	170 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGDSYHSAMDV (SEQ ID NO: 2165)
1013F03	1037	137138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013F04	1038	147148 - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1013F07	1039	145147 - 260	145 - 260	170 - 185	201 - 207	240 - 249	1 - 129	26 - 35	50 - 66	99 - 118	AATTSQKHKNYAYFYGYMDV (SEQ ID NO: 2131)
1013F09	1040	137138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1013F10	1041	147148 - 259	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1013H04	1042	147148 - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1013H07	1043	147148 - 259	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWRYYHYMDV (SEQ ID NO: 2809)

1014A12	1044	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
1014C06	1045	141 - 254	141 - 254	164 - 177	193 - 200	233 - 243	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAEFCQI (SEQ ID NO: 2854)
1014C10	1046	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1014C12	1047	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1014E06	1048	140 - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSVGATTGALDM (SEQ ID NO: 2174)
1014F02	1049	141 - 251	141 - 251	166 - 176	192 - 198	231 - 240	1 - 125	26 - 37	52 - 67	100 - 114	AGYDPLTGYPFFDS (SEQ ID NO: 2757)
1016A08	1050	144 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	EVRYNLLTRSYLAGPLDN (SEQ ID NO: 2751)
1016A09	1051	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016C02	1052	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016C03	1053	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016C05	1054	148 - 255	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	99 - 121	VQMDSEYYDLTGINVPYYFDY (SEQ ID NO: 2132)
1016C09	1055	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016C11	1056	148 - 255	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	99 - 121	VQMDSEYYDLTGINVPYYFDY (SEQ ID NO: 2132)
1016D10	1057	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016D11	1058	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016E03	1059	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016E04	1060	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016F03	1061	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016F11	1062	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016G01	1063	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016G06	1064	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1016G12	1065	148 - 255	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	99 - 121	VQMDSEYYDLTGINVPYYFDY (SEQ ID NO: 2132)
1016H10	1066	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1017A06	1067	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1017A07	1068	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1017A11	1069	140 - 253	140 - 253	162 - 175	191 - 197	233 - 242	1 - 124	25 - 34	49 - 65	98 - 113	ATYDPLTGYSFDFDI (SEQ ID NO: 2157)
1017E12	1070	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1017G03	1071	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1017G07	1072	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1017H01	1073	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018A02	1074	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018A04	1075	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EGSYDILTGYYGVGRMDV (SEQ ID NO: 2171)
1018A05	1076	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018A11	1077	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018B02	1078	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018B08	1079	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018C04	1080	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018D02	1081	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018E06	1082	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018E08	1083	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018F04	1084	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1018G06	1085	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)

1018H07	1086	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1019E05	1087	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERHYDILTGYSFDFDI (SEQ ID NO: 2784)
1019F06	1088	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERHYDILTGYSFDFDI (SEQ ID NO: 2784)
1019G12	1089	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1020D01	1090	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	DRETKVGYGMDV (SEQ ID NO: 2945)
1020D05	1091	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1020E10	1092	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1020G12	1093	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1020H06	1094	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYHILTGYSFDFDI (SEQ ID NO: 2896)
1020H10	1095	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2903)
1021A11	1096	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1021B01	1097	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1021C11	1098	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1021D12	1099	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	DRETKVGYGMDV (SEQ ID NO: 2945)
1021E10	1100	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1021G02	1101	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYSFDFDI (SEQ ID NO: 2158)
1022A08	1102	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1022B01	1103	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1022B10	1104	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1022C02	1105	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1022C04	1106	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1022C08	1107	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1022D06	1108	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1022E08	1109	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1022F01	1110	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1022F04	1111	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1022F12	1112	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	GDYDILTGYSFDFDI (SEQ ID NO: 2859)
1022G11	1113	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1023D01	1114	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTGYSFDFDI (SEQ ID NO: 2166)
1023D04	1115	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1024B04	1116	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	VYDILTGYSFDFDI (SEQ ID NO: 2177)
1024D01	1117	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1024F06	1118	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1024H01	1119	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1024H07	1120	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	DGYDILTGYSFDFDI (SEQ ID NO: 2135)
1025A01	1121	140 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1025A04	1122	140 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2174)
1025A07	1123	140 - 249	140 - 249	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2174)
1025B01	1124	133 - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1025B10	1125	140 - 253	140 - 253	164 - 176	192 - 198	233 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSFDFDI (SEQ ID NO: 2942)
1025B12	1126	140 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1025C07	1127	140 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)

1025D11	1128	<u>140142</u> - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1025E04	1129	<u>142</u> - 252	142 - 252	164 - 176	192 - 198	231 - 241	1 - 126	26 - 35	50 - 66	99 - 115	PLGITAVRGAKTDAFGI (SEQ ID NO: 2929)
1025E05	1130	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1025E07	1131	<u>140142</u> - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1025E10	1132	<u>141</u> - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1025F01	1133	<u>139140</u> - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1025F08	1134	<u>137138</u> - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GGSSQNFYGMIDV (SEQ ID NO: 2884)
1025G03	1135	<u>140142</u> - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1025G08	1136	<u>140141</u> - 254	140 - 254	163 - 176	192 - 198	231 - 243	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1025H02	1137	<u>144145</u> - 255	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 65	98 - 117	AGSGFHDILTGYYKGGYFDY (SEQ ID NO: 2961)
1026A01	1138	<u>141143</u> - 249	141 - 249	165 - 175	191 - 197	230 - 238	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAEFQI (SEQ ID NO: 2854)
1026B01	1139	<u>143144</u> - 254	143 - 254	166 - 178	194 - 200	233 - 243	1 - 127	26 - 35	50 - 66	99 - 116	GSVYDILTGTYKSGMGV (SEQ ID NO: 2733)
1026B06	1140	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026C06	1141	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026C10	1142	<u>138139</u> - 249	138 - 249	161 - 174	190 - 196	229 - 238	1 - 122	26 - 34	49 - 65	98 - 111	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1026C11	1143	<u>141</u> - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1026D09	1144	<u>139140</u> - 252	139 - 252	162 - 175	191 - 197	230 - 241	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1026E04	1145	<u>140142</u> - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1026E06	1146	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	GYDDILTGYMALDY (SEQ ID NO: 2821)
1026E09	1147	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026F01	1148	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026F09	1149	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026F12	1150	<u>140141</u> - 256	140 - 256	163 - 176	192 - 202	237 - 245	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026G08	1151	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026G10	1152	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1026G11	1153	<u>143144</u> - 255	143 - 255	166 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYYMGSAFDQ (SEQ ID NO: 2800)
1026H02	1154	<u>139140</u> - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1026H06	1155	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1026H10	1156	<u>144145</u> - 255	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	GGEYDILTGYYFGLGVYDY (SEQ ID NO: 2170)
1027A09	1157	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027B02	1158	<u>139140</u> - 250	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1027B05	1159	<u>140141</u> - 250	140 - 250	163 - 176	192 - 198	230 - 239	1 - 122	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027C08	1160	<u>138139</u> - 249	138 - 249	161 - 174	190 - 196	229 - 238	1 - 122	26 - 34	49 - 63	96 - 111	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027D02	1161	<u>141142</u> - 250	141 - 250	164 - 174	190 - 196	229 - 239	1 - 125	26 - 35	50 - 66	99 - 114	DPFGAVPGYYYAMDV (SEQ ID NO: 2826)
1027E03	1162	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027E05	1163	<u>140142</u> - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1027F04	1164	<u>144145</u> - 252	144 - 252	167 - 176	192 - 198	231 - 241	1 - 128	26 - 35	50 - 66	99 - 117	GPWYDPLFPSPGRHYGLDV (SEQ ID NO: 2793)
1027F05	1165	<u>140141</u> - 254	140 - 254	163 - 176	192 - 198	231 - 243	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1027F11	1166	<u>140141</u> - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1027G06	1167	<u>140142</u> - 253	140 - 253	164 - 176	192 - 198	233 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
1027G07	1168	<u>140142</u> - 250	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1027H03	1169	<u>141142</u> - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPAEFQI (SEQ ID NO: 2854)

1028A04	1170	143-250	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DMYYDILTGYYTGLAFDM (SEQ ID NO: 2880)
1028A07	1171	141-251	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	VLNYDILTGYYYGMDV (SEQ ID NO: 2832)
1028B08	1172	141-251	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1028B10	1173	148-258	148-258	170-183	199-205	238-247	1-132	26-35	50-68	101-121	DFGYDILTGYYIGAFYAFDI (SEQ ID NO: 2861)
1028C01	1174	142-250	142-250	165-175	191-197	230-239	1-126	26-37	52-69	102-115	GGHTCIPTCHMGG (SEQ ID NO: 2796)
1028C04	1175	143-253	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DMYYDILTGYYTGLAFDM (SEQ ID NO: 2880)
1028C08	1176	141-251	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1028D04	1177	140-247	140-247	163-173	189-195	228-236	1-124	26-35	50-65	98-113	ATQDILTGLYSGMDV (SEQ ID NO: 2977)
1028D05	1178	141-248	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	EHYDILTGYSLLGMDV (SEQ ID NO: 2907)
1028D12	1179	143-250	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DGYDILTGYSVYVGMDV (SEQ ID NO: 2938)
1028E06	1180	143-253	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116	EGSYDILTGYYVGVRMDV (SEQ ID NO: 2171)
1028E07	1181	141-248	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1028E08	1182	141-248	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1028F06	1183	146-256	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	DDRGYYDILTGYYRFGSFDI (SEQ ID NO: 2901)
1028F08	1184	134-244	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107	DIDIGGDDS (SEQ ID NO: 2954)
1028G08	1185	141-251	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	VSGYNSGYFESYDMDV (SEQ ID NO: 2732)
1028G09	1186	144-254	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
1028H10	1187	141-251	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1028H02	1188	142-249	142-249	165-175	191-197	230-238	1-126	26-37	52-69	102-115	SGEPCITLACNLGG (SEQ ID NO: 2797)
1028H03	1189	148-256	148-256	169-179	195-201	234-245	1-132	26-35	50-66	99-121	DASEYDILTGYYLATGRNWFD (SEQ ID NO: 2888)
1028H06	1190	145-255	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-118	DPSYYDILTGYYFLPYMDV (SEQ ID NO: 2843)
1028H09	1191	140-250	140-250	162-175	191-197	230-239	1-124	26-35	50-68	101-113	EIDDILTGYYMDV (SEQ ID NO: 2905)
1029A10	1192	139-246	139-246	160-170	186-192	225-235	1-123	26-35	50-65	98-112	MNYDILTGLVNWFD (SEQ ID NO: 2786)
1029A12	1193	137-247	137-247	159-171	187-193	226-236	1-121	26-35	50-68	101-110	RDLTGFDYS (SEQ ID NO: 2933)
1029B11	1194	141-251	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1029C08	1195	144-254	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGSYDILTGYYVGVRMDV (SEQ ID NO: 2171)
1029E10	1196	144-254	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
1029F08	1197	144-254	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)
1029G08	1198	141-248	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	GYDILTGYSQDAFDI (SEQ ID NO: 2927)
1030A02	1199	142-253	142-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115	TERFGAKDVTARWGMVDV (SEQ ID NO: 2874)
1030A03	1200	140-252	140-252	163-175	191-197	230-242	1-124	26-35	50-66	99-113	ENYDILTGYYNFFDY (SEQ ID NO: 2737)
1030A04	1201	140-252	140-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113	RQYDILTGYYGGFDY (SEQ ID NO: 2958)
1030A05	1202	140-249	140-249	163-175	191-197	230-238	1-123	26-35	50-66	99-112	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1030A09	1203	139-250	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1030A12	1204	139-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1030B06	1205	139-249	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1030B08	1206	140-247	140-247	163-173	189-195	228-236	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1030B10	1207	141-251	141-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114	ELGHREGGYWYSPYNV (SEQ ID NO: 2838)
1030C03	1208	139-252	139-252	162-175	191-197	230-241	1-123	26-35	50-66	99-112	RYGDPFYYYMMNV (SEQ ID NO: 2755)
1030C06	1209	146-256	146-256	169-182	198-204	237-245	1-130	26-35	50-68	101-119	DPGNYDILTGYYYYGMDV (SEQ ID NO: 2935)
1030C08	1210	133-244	133-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	SGPGWFDP (SEQ ID NO: 2870)
1030C09	1211	140-251	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)

1030C10	1212	<u>140141</u> - 250	140 - 250	163 - 175	191 - 197	230 - 239	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030C11	1213	<u>139140</u> - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030C12	1214	<u>133134</u> - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	SGPGWDFP (SEQ ID NO: 2870)
1030D07	1215	<u>139141</u> - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030D12	1216	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030E02	1217	<u>139140</u> - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030E05	1218	<u>140142</u> - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030E07	1219	<u>140142</u> - 251	140 - 251	165 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030E08	1220	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030E09	1221	<u>140141</u> - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030E10	1222	<u>139140</u> - 250	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030F02	1223	<u>141142</u> - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 37	52 - 67	100 - 114	AGYDLLTGYPFYFDS (SEQ ID NO: 2757)
1030F05	1224	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030F06	1225	<u>139140</u> - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030F08	1226	<u>140141</u> - 254	140 - 254	163 - 176	192 - 198	231 - 243	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030F09	1227	<u>140142</u> - 253	140 - 253	164 - 176	192 - 198	231 - 242	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030F11	1228	<u>139140</u> - 250	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030F12	1229	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
1030G03	1230	<u>140141</u> - 256	140 - 256	163 - 176	192 - 202	237 - 245	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030G07	1231	<u>139140</u> - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYYYMNV (SEQ ID NO: 2755)
1030G09	1232	<u>140142</u> - 251	140 - 251	164 - 174	190 - 196	229 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1030H05	1233	<u>145146</u> - 255	145 - 255	168 - 181	197 - 203	236 - 244	1 - 129	26 - 35	50 - 66	99 - 118	DRGGNYDILTGYYFHGGVDV (SEQ ID NO: 2914)
1030H06	1234	<u>146148</u> - 258	146 - 258	170 - 182	198 - 204	239 - 247	1 - 130	26 - 37	52 - 69	102 - 119	ATKSYDILTRMYYHYHMDV (SEQ ID NO: 2748)
1030H10	1235	<u>140141</u> - 253	140 - 253	163 - 176	192 - 198	231 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNYDILTGYSRRFDP (SEQ ID NO: 2942)
1030H11	1236	<u>140142</u> - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1031A01	1237	<u>137138</u> - 248	137 - 248	160 - 173	189 - 195	228 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031A03	1238	<u>141143</u> - 251	141 - 251	166 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	PYYDPLTAYTFQYFGN (SEQ ID NO: 2806)
1031A08	1239	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031A12	1240	<u>146147</u> - 257	146 - 257	169 - 181	197 - 203	236 - 246	1 - 130	26 - 35	50 - 66	99 - 119	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2972)
1031B03	1241	<u>136137</u> - 246	136 - 246	159 - 172	188 - 194	227 - 235	1 - 120	26 - 35	50 - 68	101 - 109	GLGHTSDS (SEQ ID NO: 2959)
1031B06	1242	<u>142143</u> - 253	142 - 253	165 - 177	193 - 199	232 - 242	1 - 126	26 - 35	50 - 66	99 - 115	AKGYYYDSSGASDVFDV (SEQ ID NO: 2871)
1031B07	1243	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031B08	1244	<u>147149</u> - 260	147 - 260	171 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1031B09	1245	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SNPPKWYDALTGHSYHSAMDV (SEQ ID NO: 2840)
1031B11	1246	<u>137138</u> - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031B12	1247	<u>147148</u> - 259	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031C01	1248	<u>137138</u> - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031C02	1249	<u>141142</u> - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	PFYDILTSYVFQYFDH (SEQ ID NO: 2137)
1031C04	1250	<u>147149</u> - 260	147 - 260	171 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	GRKDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2813)
1031C08	1251	<u>137139</u> - 248	137 - 248	161 - 171	187 - 193	226 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031C11	1252	<u>147149</u> - 257	147 - 257	171 - 181	197 - 203	236 - 246	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031D01	1253	<u>145146</u> - 256	145 - 256	168 - 180	196 - 202	235 - 245	1 - 129	26 - 35	50 - 66	99 - 118	AATTSQKHNKYAYFYGMDV (SEQ ID NO: 2131)

1031D04	1254	<u>137138</u> - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031D06	1255	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKLWDRYYHYHYMDV (SEQ ID NO: 2807)
1031D08	1256	<u>144145</u> - 257	144 - 257	167 - 180	196 - 202	235 - 246	1 - 128	26 - 35	50 - 66	99 - 117	VRPKLYFDWLSRHDAFDL (SEQ ID NO: 2820)
1031D09	1257	<u>137139</u> - 247	137 - 247	161 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031D11	1258	<u>147149</u> - 256	147 - 256	171 - 181	197 - 203	236 - 245	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTDGSSYHSAMDV (SEQ ID NO: 2165)
1031D12	1259	<u>144146</u> - 254	144 - 254	168 - 178	194 - 200	233 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DKAHGEYGRDYHYHYMDV (SEQ ID NO: 2735)
1031E01	1260	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTDGSSYHSAMDV (SEQ ID NO: 2159)
1031E05	1261	<u>147149</u> - 257	147 - 257	171 - 181	197 - 203	236 - 246	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTDGSSYHSAMDV (SEQ ID NO: 2159)
1031E07	1262	<u>147148</u> - 259	147 - 259	170 - 182	198 - 204	237 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTDGSSYHSAMDV (SEQ ID NO: 2159)
1031E08	1263	<u>147148</u> - 259	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031E09	1264	<u>137139</u> - 246	137 - 246	162 - 173	189 - 195	228 - 235	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031E10	1265	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTDGSSYHSAMDV (SEQ ID NO: 2165)
1031E11	1266	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTDGSSYHSAMDV (SEQ ID NO: 2159)
1031F01	1267	<u>137138</u> - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031F04	1268	<u>137139</u> - 246	137 - 246	162 - 172	188 - 194	227 - 235	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031F06	1269	<u>135137</u> - 247	135 - 247	159 - 171	187 - 193	226 - 236	1 - 119	26 - 35	50 - 66	99 - 108	DTVRSGGMDV (SEQ ID NO: 2804)
1031F10	1270	<u>147148</u> - 259	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031F11	1271	<u>144145</u> - 255	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	DKAHGEYGRDYHYHYMDV (SEQ ID NO: 2735)
1031F12	1272	<u>137138</u> - 249	137 - 249	160 - 172	188 - 194	227 - 238	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031G01	1273	<u>137138</u> - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031G03	1274	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTDGSSYHSAMDV (SEQ ID NO: 2159)
1031G05	1275	<u>147148</u> - 259	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031G06	1276	<u>147148</u> - 258	147 - 258	170 - 182	198 - 204	237 - 247	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031G07	1277	<u>147149</u> - 259	147 - 259	171 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTDGSSYHSAMDV (SEQ ID NO: 2816)
1031G09	1278	<u>147148</u> - 263	147 - 263	170 - 183	199 - 209	244 - 252	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031G12	1279	<u>145146</u> - 256	145 - 256	168 - 180	196 - 202	235 - 245	1 - 129	26 - 35	50 - 66	99 - 118	AATTSQKHNYAYFYGMDV (SEQ ID NO: 2131)
1031H01	1280	<u>137138</u> - 250	137 - 250	160 - 173	189 - 195	228 - 239	1 - 121	26 - 35	50 - 66	99 - 110	GYDSSAFRAFDI (SEQ ID NO: 2136)
1031H02	1281	<u>142143</u> - 255	142 - 255	165 - 178	194 - 200	233 - 244	1 - 126	26 - 35	50 - 66	99 - 115	AKGYYDSSGASDVFDV (SEQ ID NO: 2871)
1031H03	1282	<u>147148</u> - 260	147 - 260	170 - 183	199 - 205	238 - 249	1 - 131	26 - 35	50 - 66	99 - 120	GREDTDKVKPWDRYYHYHYMDV (SEQ ID NO: 2809)
1031H06	1283	<u>144145</u> - 257	144 - 257	167 - 179	195 - 201	234 - 246	1 - 128	26 - 35	50 - 66	99 - 117	DKAHGEYGRDYHYHYMDV (SEQ ID NO: 2735)
1031H09	1284	<u>144145</u> - 255	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	DKAHGEYGRDYHYHYMDV (SEQ ID NO: 2735)
1031H10	1285	<u>143144</u> - 256	143 - 256	166 - 179	195 - 201	234 - 245	1 - 127	26 - 35	50 - 66	99 - 116	DRGYTGYDLVGGYFDF (SEQ ID NO: 2931)
1031H11	1286	<u>135136</u> - 246	135 - 246	158 - 170	186 - 192	225 - 235	1 - 119	26 - 35	50 - 66	99 - 108	DTVRSGGMDV (SEQ ID NO: 2804)
1033A08	1287	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYHYGMDV (SEQ ID NO: 2129)
1033B11	1288	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 37	52 - 69	102 - 117	DRYDILTGYYHYGMDV (SEQ ID NO: 2129)
1033C01	1289	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRYNDDLTRSYLAGPLDN (SEQ ID NO: 2751)
1033C08	1290	<u>142141</u> - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	EMGYDILTGYYLNYMDV (SEQ ID NO: 2862)
1033D02	1291	138 - 245	138 - 245	161 - 171	187 - 193	226 - 234	1 - 122	26 - 35	50 - 66	99 - 111	GDYDILTGYYMDV (SEQ ID NO: 2781)
1033D03	1292	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1033D05	1293	<u>141140</u> - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1033D11	1294	<u>140139</u> - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	VKRDILTGVEGMDV (SEQ ID NO: 2869)
1033D12	1295	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	GGPHYDILTGYYMAVGFDI (SEQ ID NO: 2962)

1033E01	1296	139 - 249	139 - 249	161 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	DIDARLAALDAFDI (SEQ ID NO: 2794)
1033E06	1297	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATHDPLTGYSFDFDI (SEQ ID NO: 2780)
1033E11	1298	143 - 253	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	HRSRCSSTSCRNDAFDI (SEQ ID NO: 2770)
1033E12	1299	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	EMGYDILTGYYLNYMDV (SEQ ID NO: 2862)
1033F03	1300	139 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	EGAADYLNQYFQD (SEQ ID NO: 2768)
1033F08	1301	145 - 256	145 - 256	167 - 179	195 - 201	234 - 245	1 - 129	26 - 35	50 - 66	99 - 118	QKVVYDILTGNYYYGYGMDV (SEQ ID NO: 2767)
1033F10	1302	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRNYDLTRSYLAGPLDN (SEQ ID NO: 2751)
1033F12	1303	134 - 241	134 - 241	155 - 165	181 - 187	220 - 230	1 - 118	26 - 35	50 - 66	99 - 107	DIDIIGDDSS (SEQ ID NO: 2954)
1033G01	1304	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)
1033G03	1305	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	PQGVTLVRGAETDAFAI (SEQ ID NO: 2925)
1033G08	1306	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1033H04	1307	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	49 - 65	98 - 113	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1037A05	1308	139 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLPFHYGMDV (SEQ ID NO: 2133)
1037B03	1309	141 - 251	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTRLNYYWFDL (SEQ ID NO: 2950)
1037B04	1310	144 - 251	144 - 251	167 - 177	193 - 199	232 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DPGYDILTGYPHYGMDV (SEQ ID NO: 2922)
1037C04	1311	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 65	98 - 115	ENGDDYDILTGQTFYGMDV (SEQ ID NO: 2752)
1037C06	1312	141 - 249	141 - 249	163 - 173	189 - 195	228 - 238	1 - 125	26 - 35	50 - 66	99 - 114	LYYDILTGYPHYGMDV (SEQ ID NO: 2882)
1037C08	1313	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DGIDILVPAALMDV (SEQ ID NO: 2160)
1037D11	1314	136 - 246	136 - 246	158 - 171	187 - 193	226 - 235	1 - 120	26 - 35	50 - 66	99 - 109	SQWLEHDFDI (SEQ ID NO: 2864)
1037E06	1315	144 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	DRRDYDLTRYYYYGYGMDV (SEQ ID NO: 2928)
1037F04	1316	144 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 65	98 - 117	KQRGDYDILTGQYGYAFDI (SEQ ID NO: 2808)
1037G01	1317	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTRLNYYWFDL (SEQ ID NO: 2950)
1037G03	1318	146 - 256	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 66	99 - 119	DLGSFYDILTALRLNYYGMDV (SEQ ID NO: 2963)
1037G10	1319	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DYYDILTKLPYGMDV (SEQ ID NO: 2975)
1042A07	1320	144 - 251	144 - 251	167 - 177	193 - 199	232 - 240	1 - 128	26 - 35	50 - 66	99 - 117	VSPSYDILTGYYLPHAFDV (SEQ ID NO: 2849)
1042A10	1321	142 - 249	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 65	98 - 115	GPYYDILTGYYRNWFDV (SEQ ID NO: 2801)
1042B03	1322	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	DIDILTGYYLGMVDV (SEQ ID NO: 2924)
1042B12	1323	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTRLNYYWFDL (SEQ ID NO: 2166)
1042D01	1324	136 - 246	136 - 246	158 - 171	187 - 193	226 - 235	1 - 120	26 - 35	50 - 66	99 - 109	QQWLPYDAFDI (SEQ ID NO: 2839)
1042D03	1325	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 68	101 - 113	AYYDILTGYYFFDI (SEQ ID NO: 2873)
1042D10	1326	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 65	98 - 115	ERADYDILTGYYFYGMDV (SEQ ID NO: 2802)
1042E10	1327	147 - 257	147 - 257	169 - 182	198 - 204	237 - 246	1 - 131	26 - 37	52 - 69	102 - 120	ERPYYDILTGYYTVTYGMDV (SEQ ID NO: 2798)
1042E11	1328	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	DEYDILTLGQGMVDV (SEQ ID NO: 2883)
1042F08	1329	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 37	52 - 67	100 - 115	GDYDILTGYPPLHAFDI (SEQ ID NO: 2738)
1042F12	1330	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	DGYDILTGYYFGMDV (SEQ ID NO: 2976)
1042G08	1331	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	EHYDILTGYSLLGMVDV (SEQ ID NO: 2907)
1042G10	1332	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SHYDILTRLNYYWFDL (SEQ ID NO: 2166)
1042H03	1333	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	GSLYYDILTGYYIGNAFAI (SEQ ID NO: 2759)
1043A03	1334	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DGYDILTGYYFYGMDV (SEQ ID NO: 2899)
1043B02	1335	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 65	98 - 115	GGYYDILTGYYLVYYGMDV (SEQ ID NO: 2744)
1043B03	1336	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1043B06	1337	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DQYDILTGYYHIDYYMDV (SEQ ID NO: 2828)

1043B07	1338	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1043B09	1339	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	HVRDYDILTGYYRGHFDY (SEQ ID NO: 2727)
1043D11	1340	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRYNDLLTRSYLAGPLDN (SEQ ID NO: 2751)
1043E05	1341	143 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	TESRNYDILTGYYWPSMDV (SEQ ID NO: 2940)
1043F01	1342	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1043F04	1343	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1043F12	1344	143 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	TESRNYDILTGYYWPSMDV (SEQ ID NO: 2940)
1043H07	1345	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1044A11	1346	144 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 68	101 - 117	APYDILTGYSFDFDI (SEQ ID NO: 2968)
1044B11	1347	139 - 249	139 - 249	161 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	DSARLAALDAFDI (SEQ ID NO: 2978)
1044C09	1348	140 - 250	140 - 250	162 - 174	190 - 196	229 - 239	1 - 124	26 - 35	50 - 66	99 - 113	GQFGLPNYYYHMDV (SEQ ID NO: 2943)
1044C10	1349	143 - 253	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DIKRYNSNWPYYDYMDV (SEQ ID NO: 2726)
1044D03	1350	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DKQYYDILTGDPVEGMDV (SEQ ID NO: 2889)
1044D09	1351	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1044E07	1352	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSSLVTYGTVD (SEQ ID NO: 2825)
1044E11	1353	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	SDDYDILTGNYVGSLLDY (SEQ ID NO: 2758)
1044F07	1354	147 - 257	147 - 257	169 - 182	198 - 204	237 - 246	1 - 131	26 - 35	50 - 66	99 - 120	DGRLSYDILTGYYARDYYGMDV (SEQ ID NO: 2912)
1044G02	1355	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1044G07	1356	149 - 259	149 - 259	171 - 184	200 - 206	239 - 248	1 - 133	26 - 35	50 - 66	99 - 122	DQNHPYDILTGYYVPTGPLEKN (SEQ ID NO: 2845)
1044H01	1357	144 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 65	99 - 117	EVRYNDLLTRSYLAGPLDN (SEQ ID NO: 2751)
1050A01	1358	141 - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	DMGYDILTGYYGAFDI (SEQ ID NO: 2946)
1050B12	1359	141 - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	DYYDVLTFGSLDGMVD (SEQ ID NO: 2829)
1050C06	1360	140 - 248	140 - 248	165 - 175	191 - 197	230 - 237	1 - 124	26 - 35	50 - 65	98 - 113	DHYDVLTFGSLQAFDV (SEQ ID NO: 2728)
1050C08	1361	141 - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 37	52 - 67	100 - 114	GRYDFTGYYLRFNDY (SEQ ID NO: 2731)
1050E01	1362	140 - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 35	50 - 66	99 - 113	GHYDILTGYYFGFDY (SEQ ID NO: 2886)
1050E10	1363	137 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	DMKVYKYALDV (SEQ ID NO: 2823)
1050H08	1364	141 - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	DLRYDILTGYYHDAFDI (SEQ ID NO: 2890)
1051A04	1365	147 - 258	147 - 258	170 - 183	199 - 205	238 - 247	1 - 131	26 - 35	50 - 66	99 - 120	SSPPKWYDALTGHSYHSAMDV (SEQ ID NO: 2159)
1051A08	1366	141 - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	HRRARVVVPVPGAMDV (SEQ ID NO: 2930)
1051A12	1367	143 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
1051B08	1368	142 - 253	142 - 253	165 - 177	193 - 199	232 - 242	1 - 126	26 - 36	51 - 67	100 - 115	RSMIVVTTAPYDAFDL (SEQ ID NO: 2785)
1051C06	1369	135 - 246	135 - 246	158 - 170	186 - 192	225 - 235	1 - 119	26 - 35	50 - 66	99 - 108	DTVRSGGMDV (SEQ ID NO: 2804)
1051G12	1370	143 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
1055A05	1371	133 - 244	133 - 244	156 - 169	185 - 191	224 - 233	1 - 117	26 - 35	50 - 66	99 - 106	SGPGWFDP (SEQ ID NO: 2870)
1055A11	1372	133 - 244	133 - 244	156 - 169	185 - 191	224 - 233	1 - 117	26 - 35	50 - 66	99 - 106	SGPGWFDP (SEQ ID NO: 2870)
1061A03	1373	140 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGSSIVGATTGALDM (SEQ ID NO: 2852)
1061A04	1374	141 - 251	141 - 251	165 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	GDYDILTGYPACFCQI (SEQ ID NO: 2854)
1061A08	1375	140 - 253	140 - 253	164 - 176	192 - 198	232 - 242	1 - 124	26 - 35	50 - 66	99 - 113	DNVDILTGYSRRFDP (SEQ ID NO: 2942)
1061A09	1376	140 - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1061A10	1377	140 - 249	140 - 249	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1061B07	1378	140 - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1061B09	1379	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	24 - 33	48 - 64	97 - 116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO: 2158)

1061B12	1380	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1061C12	1381	138 - 248	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	99 - 111	TYDYDILTGYPHFY (SEQ ID NO: 2788)
1061D01	1382	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 68	101 - 110	GPGVIGNYDY (SEQ ID NO: 2749)
1061D03	1383	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1061D04	1384	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	AVLRYSAGLQAFDI (SEQ ID NO: 2970)
1061D07	1385	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	VSGYNSGYPESYDMDV (SEQ ID NO: 2732)
1061D09	1386	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	LNLEKTVVRGFGYFDL (SEQ ID NO: 2952)
1061D10	1387	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	DHYDILTGLYYGMDV (SEQ ID NO: 2760)
1061E01	1388	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	LNLEKTVVRGFGYFDL (SEQ ID NO: 2952)
1061E05	1389	142 - 251	142 - 251	163 - 175	191 - 197	230 - 240	1 - 126	26 - 35	50 - 66	99 - 115	GGLVWFGESDYGYGMDV (SEQ ID NO: 2787)
1061E09	1390	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1061E12	1391	133 - 240	133 - 240	154 - 164	180 - 186	219 - 229	1 - 117	26 - 35	50 - 66	99 - 106	SQRLFIDS (SEQ ID NO: 2842)
1061F01	1392	146 - 256	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 66	99 - 119	DRYDILTGYYIPGLDADF (SEQ ID NO: 2887)
1061F09	1393	139 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	DSARLAALDAF (SEQ ID NO: 2978)
1061F10	1394	145 - 252	145 - 252	166 - 176	192 - 198	231 - 241	1 - 129	26 - 35	50 - 66	99 - 118	EESYYDILTGYYHYGMDV (SEQ ID NO: 2743)
1061F11	1395	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYYFDFDI (SEQ ID NO: 2949)
1061G01	1396	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1061G03	1397	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	AYYDILTGFLPYMDL (SEQ ID NO: 2771)
1061G09	1398	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRYDILLTRSYLAGPLDN (SEQ ID NO: 2751)
1061G10	1399	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	EGSYDILTGYYGVGMDV (SEQ ID NO: 2171)
1061G11	1400	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 68	101 - 110	RDILTGFDYS (SEQ ID NO: 2933)
1061H05	1401	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 37	52 - 67	100 - 115	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1064A05	1402	142 - 252	142 - 252	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 68	101 - 115	DFYDILTGYPHFY (SEQ ID NO: 2919)
1064A11	1403	138 - 248	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	99 - 111	HSKEYNWNALDY (SEQ ID NO: 2754)
1064B01	1404	138 - 248	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	99 - 111	TRMDVLTGYYHDAF (SEQ ID NO: 2750)
1064B02	1405	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	AFEDYDILTGYYHDAF (SEQ ID NO: 2911)
1064B12	1406	133 - 243	133 - 243	155 - 168	184 - 190	223 - 232	1 - 117	26 - 35	50 - 66	99 - 106	PSYHYMDV (SEQ ID NO: 2740)
1064C06	1407	145 - 255	145 - 255	167 - 180	196 - 202	235 - 244	1 - 129	26 - 35	50 - 66	99 - 118	VNADYDILTGPRDYGYMDV (SEQ ID NO: 2819)
1064D01	1408	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1064D02	1409	146 - 256	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 66	99 - 119	EDATYDILTGYYMGSGMDV (SEQ ID NO: 2763)
1064E01	1410	143 - 250	143 - 250	166 - 176	192 - 198	231 - 239	1 - 127	26 - 35	50 - 66	99 - 116	ETRYTSSPPYNYGYMDV (SEQ ID NO: 2736)
1064E02	1411	140 - 251	140 - 251	162 - 174	190 - 196	229 - 240	1 - 124	26 - 35	50 - 66	99 - 113	RDYDILTGYSRDFP (SEQ ID NO: 2725)
1064E03	1412	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DGIYDILTLVSYNGMDV (SEQ ID NO: 2775)
1064E07	1413	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 65	98 - 113	GERDILTGYYLDGMDV (SEQ ID NO: 2948)
1064E08	1414	140 - 250	140 - 250	162 - 174	190 - 196	229 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ERGSYSSGSGAFDV (SEQ ID NO: 2898)
1064F05	1415	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	ESGGYSYSGRDYGYMDV (SEQ ID NO: 2836)
1064F08	1416	145 - 252	145 - 252	166 - 176	192 - 198	231 - 241	1 - 129	26 - 35	50 - 66	99 - 118	DRGVGYDILTGRTYYGYMDV (SEQ ID NO: 2900)
1064G06	1417	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065A12	1418	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DVSGHDILTGYSRYFDV (SEQ ID NO: 2795)
1065C04	1419	139 - 249	139 - 249	161 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	GQKNYESSGYLEH (SEQ ID NO: 2916)
1065C09	1420	140 - 250	140 - 250	162 - 174	190 - 196	229 - 239	1 - 124	26 - 35	50 - 66	99 - 113	GDYDILTGYSHFY (SEQ ID NO: 2908)
1065E02	1421	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	AYDYDILTGYSYFY (SEQ ID NO: 2895)

1065E04	1422	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1065F03	1423	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1065G06	1424	135134 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1065G07	1425	142141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GGNYDILTGYYIGAFDI (SEQ ID NO: 2824)
1065G08	1426	139138 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	GNLLLPHYGMDV (SEQ ID NO: 2133)
1065H06	1427	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	GYYEYDILTGYNELGAFDI (SEQ ID NO: 2851)
1066A03	1428	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DGTYDILTGYYNQYGMVDV (SEQ ID NO: 2915)
1066A08	1429	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1066A09	1430	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1066A10	1431	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	DRGYDILTGYYYGMDV (SEQ ID NO: 2876)
1066A11	1432	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	EVRDYDILTGYYISYMDV (SEQ ID NO: 2778)
1066B02	1433	135134 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1066B08	1434	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1066B10	1435	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	GLYFEDTNYRHGDAFDI (SEQ ID NO: 2790)
1066C02	1436	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1066C11	1437	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1066C12	1438	135134 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1066D06	1439	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ENYDFLTGYYGAFDI (SEQ ID NO: 2772)
1066D08	1440	138 - 248	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	99 - 111	HSKEYNWNALDY (SEQ ID NO: 2754)
1066D11	1441	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	ERSQDFLTGVDRYHPMDV (SEQ ID NO: 2956)
1066D12	1442	139 - 249	139 - 249	161 - 174	190 - 196	229 - 238	1 - 123	26 - 35	50 - 66	99 - 112	EGAADYLNQYFQH (SEQ ID NO: 2815)
1066E06	1443	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1066E12	1444	135134 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1066G05	1445	142141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GLYFEDTNYRHGDAFDI (SEQ ID NO: 2790)
1066G08	1446	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	VYYDILTGHTPYGMDV (SEQ ID NO: 2791)
1066G10	1447	144 - 254	144 - 254	166 - 178	194 - 200	233 - 243	1 - 128	26 - 35	50 - 68	99 - 116	GIYDILTGYYWDDAFDI (SEQ ID NO: 2872)
1066G12	1448	143 - 254	143 - 254	165 - 177	193 - 199	232 - 243	1 - 127	26 - 35	50 - 66	99 - 116	ESTYDILTGSYHDYGLDV (SEQ ID NO: 2822)
1066H04	1449	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	DRLHYDILTGHTQDDAFDI (SEQ ID NO: 2885)
1067A07	1450	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	VLTYDILTGYYREDAFDM (SEQ ID NO: 2939)
1067A11	1451	135 - 245	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1067B08	1452	149 - 259	149 - 259	171 - 184	200 - 206	239 - 248	1 - 133	26 - 35	50 - 66	99 - 122	DRGASNYDILTGYYAPAQGVAFDI (SEQ ID NO: 2969)
1067C08	1453	148 - 258	148 - 258	170 - 183	199 - 205	238 - 247	1 - 132	26 - 37	52 - 69	102 - 121	EGAHYDILTGHNYYHYGMDV (SEQ ID NO: 2747)
1067C09	1454	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	ETRKYTSSPPYNYYYMDV (SEQ ID NO: 2736)
1067D07	1455	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1067E01	1456	140142 - 248	140 - 248	164 - 174	190 - 196	229 - 238	1 - 124	26 - 35	50 - 66	99 - 113	DQHDILTGYYYGMDV (SEQ ID NO: 2921)
1067E06	1457	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1067E07	1458	150 - 260	150 - 260	172 - 184	200 - 206	239 - 249	1 - 134	26 - 35	50 - 67	100 - 123	DYPGSEYDILTGLYFGYYYYGMDV (SEQ ID NO: 2926)
1067E11	1459	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1067G03	1460	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ARRVGLVGKNAFEI (SEQ ID NO: 2765)
1067G05	1461	140 - 250	140 - 250	162 - 174	190 - 196	229 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DQHDILTGYYYGMDV (SEQ ID NO: 2894)
1067G12	1462	141 - 252	141 - 252	163 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1067H05	1463	146 - 256	146 - 256	168 - 180	196 - 202	235 - 245	1 - 130	26 - 35	50 - 68	101 - 119	EGTYDILTGYYPLGYFDY (SEQ ID NO: 2936)

1067H06	1464	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1068C09	1465	137 138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	GGSSQNFYGMVDV (SEQ ID NO: 2884)
1068G03	1466	143 144 - 254	143 - 254	166 - 178	194 - 200	233 - 243	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1068G04	1467	142 143 - 252	142 - 252	165 - 178	194 - 200	233 - 241	1 - 126	26 - 35	50 - 66	99 - 115	GVVWYAGDVGIYGFVDV (SEQ ID NO: 2937)
1068G07	1468	140 142 - 251	140 - 251	164 - 174	190 - 196	229 - 240	1 - 124	26 - 35	50 - 66	99 - 113	HDYIMTAHHYYDS (SEQ ID NO: 2909)
1068G08	1469	143 144 - 254	143 - 254	166 - 178	194 - 200	233 - 243	1 - 127	26 - 35	50 - 66	99 - 116	GIGYDLLTGYFTGSPLDY (SEQ ID NO: 2846)
1070F07	1470	140 139 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	DFYDILTGYHDAFDI (SEQ ID NO: 2910)
1070G05	1471	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 68	101 - 113	DVDDILTGYSDY (SEQ ID NO: 2867)
1070H02	1472	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1071A01	1473	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	AAVDPLTGYSFDFDI (SEQ ID NO: 2783)
1071A03	1474	143 142 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DMHYDILTGYTGLAFDM (SEQ ID NO: 2917)
1071B08	1475	142 144 - 252	142 - 252	166 - 176	192 - 198	231 - 241	1 - 126	27 - 36	51 - 67	100 - 115	GGYDILTQYPAEFFHP (SEQ ID NO: 2764)
1071E01	1476	138 - 248	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	99 - 111	DFGVIGDYRPFY (SEQ ID NO: 2777)
1071F11	1477	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	SSNPVYGLDV (SEQ ID NO: 2957)
1071G11	1478	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1071H08	1479	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1074A02	1480	141 142 - 250	141 - 250	164 - 174	190 - 196	229 - 239	1 - 125	26 - 35	50 - 66	99 - 114	DDRDILTNYLYEFQH (SEQ ID NO: 2868)
1074A08	1481	147 148 - 259	147 - 259	170 - 182	198 - 204	237 - 248	1 - 131	26 - 35	50 - 66	99 - 120	SSPKWYDALTGSSYHSAMDV (SEQ ID NO: 2165)
1074D10	1482	144 146 - 253	144 - 253	168 - 178	194 - 200	233 - 242	1 - 128	26 - 35	50 - 66	99 - 117	DKTLGDQLVEAYYDGMVDV (SEQ ID NO: 2776)
1074E01	1483	144 146 - 255	144 - 255	168 - 178	194 - 200	233 - 244	1 - 128	26 - 35	50 - 66	99 - 117	LGRTSRDLLTGYHFYNMVDV (SEQ ID NO: 2944)
1074E02	1484	140 142 - 250	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DDYDILTGLSYFDS (SEQ ID NO: 2803)
1074E08	1485	143 144 - 259	143 - 259	166 - 179	195 - 205	240 - 248	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1074F12	1486	140 142 - 250	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 35	50 - 66	99 - 113	DRADILTGYNDAFDI (SEQ ID NO: 2739)
1074H06	1487	139 140 - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1074H07	1488	143 145 - 253	143 - 253	167 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	VSNDILTGWGGYNWFDP (SEQ ID NO: 2955)
1074H08	1489	142 143 - 254	142 - 254	165 - 178	194 - 200	233 - 243	1 - 126	26 - 35	50 - 66	99 - 115	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1075A07	1490	143 145 - 253	143 - 253	167 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1075B01	1491	133 134 - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075B04	1492	133 134 - 247	133 - 247	156 - 169	185 - 191	224 - 236	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075B06	1493	140 141 - 252	140 - 252	163 - 175	191 - 197	230 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1075B08	1494	143 144 - 257	143 - 257	166 - 179	195 - 201	234 - 246	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1075B09	1495	141 142 - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	TYDILTGYAAEYFQH (SEQ ID NO: 2932)
1075B12	1496	140 141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 35	50 - 66	99 - 113	SDYDILTGYWVPAV (SEQ ID NO: 2812)
1075C01	1497	147 148 - 259	147 - 259	170 - 183	199 - 205	238 - 248	1 - 131	26 - 35	50 - 66	99 - 120	GRGRTDKVKPWFDRYFHYMDV (SEQ ID NO: 2835)
1075C05	1498	133 134 - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075D05	1499	143 145 - 253	143 - 253	168 - 179	195 - 201	234 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSVFDP (SEQ ID NO: 2897)
1075D07	1500	141 142 - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	SYDILTGYHHTPLDY (SEQ ID NO: 2853)
1075D08	1501	140 141 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1075E01	1502	143 145 - 253	143 - 253	167 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1075E03	1503	148 150 - 261	148 - 261	172 - 184	200 - 206	239 - 250	1 - 132	28 - 37	52 - 68	101 - 121	GGGYDILTGYSPYLYYGLDV (SEQ ID NO: 2865)
1075E04	1504	143 144 - 255	143 - 255	166 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	GRGYDVLTYFTGSPLDY (SEQ ID NO: 2881)
1075E05	1505	140 141 - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)

1075E10	1506	<u>140141</u> - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1075E11	1507	<u>143134</u> - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	SGPGWFDP (SEQ ID NO: 2870)
1075E12	1508	<u>142143</u> - 254	142 - 254	165 - 178	194 - 200	233 - 243	1 - 126	26 - 35	50 - 66	99 - 115	TDRFGAKDVTARWGMVDV (SEQ ID NO: 2979)
1075F02	1509	<u>144146</u> - 253	144 - 253	168 - 178	194 - 200	233 - 242	1 - 128	26 - 35	50 - 66	99 - 117	EQGYDILTYYPEGGWFDP (SEQ ID NO: 2834)
1075F04	1510	<u>141142</u> - 251	141 - 251	164 - 176	192 - 198	231 - 240	1 - 125	26 - 37	52 - 67	100 - 114	AGYDILLTGYPFFYFDS (SEQ ID NO: 2757)
1075F06	1511	<u>144146</u> - 254	144 - 254	168 - 178	194 - 200	233 - 243	1 - 128	26 - 35	50 - 66	99 - 117	GRNYDFLTGYNENLGLDY (SEQ ID NO: 2830)
1075F07	1512	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	ENYDSLTCGYNYFYDY (SEQ ID NO: 2971)
1075F08	1513	<u>143134</u> - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQRKAQDI (SEQ ID NO: 2779)
1075F09	1514	<u>145147</u> - 257	145 - 257	169 - 181	197 - 203	236 - 246	1 - 129	26 - 35	50 - 66	99 - 118	LKAPYYDLITGYHLPKWFDI (SEQ ID NO: 2953)
1075F10	1515	<u>143135</u> - 243	133 - 243	157 - 167	183 - 189	222 - 232	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075F11	1516	<u>143134</u> - 245	133 - 245	156 - 169	185 - 191	224 - 234	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075G05	1517	<u>140141</u> - 252	140 - 252	163 - 175	191 - 197	230 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1075G07	1518	<u>140141</u> - 252	140 - 252	163 - 175	191 - 197	230 - 241	1 - 124	26 - 35	50 - 66	99 - 113	GRYYDMLTRGGYFDY (SEQ ID NO: 2858)
1075G08	1519	<u>140141</u> - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 35	50 - 66	99 - 113	RQYDILTGYGGYFDY (SEQ ID NO: 2958)
1075G11	1520	<u>141142</u> - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	TDYDILTGYPMGYFDP (SEQ ID NO: 2173)
1075G12	1521	<u>143134</u> - 245	133 - 245	156 - 169	185 - 191	224 - 234	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075H02	1522	<u>143144</u> - 254	143 - 254	166 - 178	194 - 200	233 - 243	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1075H03	1523	<u>143134</u> - 245	133 - 245	156 - 169	185 - 191	224 - 234	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075H06	1524	<u>143134</u> - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075H08	1525	<u>143144</u> - 254	143 - 254	166 - 179	195 - 201	234 - 243	1 - 127	26 - 35	50 - 66	99 - 116	GSGYDILTGYFTGSPLDY (SEQ ID NO: 2766)
1076A01	1526	<u>142144</u> - 253	142 - 253	166 - 176	192 - 198	231 - 242	1 - 126	26 - 35	50 - 66	99 - 115	DRRDDLTGYLYDAFDS (SEQ ID NO: 2878)
1076A03	1527	<u>143137</u> - 247	135 - 247	159 - 171	187 - 193	226 - 236	1 - 119	26 - 35	50 - 68	101 - 108	GYDTAMQY (SEQ ID NO: 2951)
1076A06	1528	<u>143134</u> - 245	133 - 245	156 - 168	184 - 190	223 - 234	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1076A07	1529	<u>140140</u> - 250	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	DRRDILTGSNFGQD (SEQ ID NO: 2913)
1076A08	1530	<u>142144</u> - 253	142 - 253	166 - 176	192 - 198	231 - 242	1 - 126	26 - 35	50 - 66	99 - 115	MGHYDILTGYRHYGMDV (SEQ ID NO: 2831)
1076B01	1531	<u>143145</u> - 257	143 - 257	167 - 179	195 - 201	236 - 246	1 - 127	26 - 35	50 - 66	99 - 116	GSGYDILTGYFTGSPLDY (SEQ ID NO: 2766)
1076B03	1532	<u>143134</u> - 245	133 - 245	156 - 169	185 - 191	224 - 234	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1076B07	1533	<u>143135</u> - 243	133 - 243	157 - 167	183 - 189	222 - 232	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1076B08	1534	<u>141143</u> - 252	141 - 252	166 - 177	193 - 199	232 - 241	1 - 125	26 - 35	50 - 66	99 - 114	PYYDPLTAYTFQYFGN (SEQ ID NO: 2806)
1076C04	1535	<u>140142</u> - 250	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1076C10	1536	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	GRYYDMLTRGGYFDY (SEQ ID NO: 2858)
1076D01	1537	<u>141142</u> - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	LDYDILTGYPSGFYDY (SEQ ID NO: 2799)
1076D08	1538	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 37	52 - 67	100 - 113	RFYDILLTGYSAFDS (SEQ ID NO: 2756)
1076D12	1539	<u>143144</u> - 255	143 - 255	166 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1076E04	1541	<u>142145</u> - 252	142 - 252	167 - 177	193 - 199	232 - 241	1 - 127	26 - 35	50 - 66	99 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1076E07	1542	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1076E09	1543	<u>141142</u> - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 113	EYDVLTLGLFYMDV (SEQ ID NO: 2841)
1076E11	1544	<u>143144</u> - 254	143 - 254	166 - 179	195 - 201	234 - 243	1 - 127	26 - 35	50 - 66	99 - 116	DRDILTNLYLEYFQH (SEQ ID NO: 2868)
1076F01	1545	<u>143144</u> - 253	143 - 253	166 - 178	194 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSADFQ (SEQ ID NO: 2800)
1076F03	1546	<u>140141</u> - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 36	51 - 66	99 - 113	GDYDVLTLGYLRKLDY (SEQ ID NO: 2742)
1076F04	1547	<u>143135</u> - 245	133 - 245	157 - 169	185 - 191	224 - 234	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)

1076F08	1548	140 142 - 250	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 36	51 - 66	99 - 113	VHYDILTGYLWAFDI (SEQ ID NO: 2730)
1076F10	1549	140 141 - 252	140 - 252	163 - 175	191 - 197	230 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1076G09	1550	133 134 - 245	133 - 245	156 - 168	184 - 190	223 - 234	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1076G10	1551	140 141 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	GRYYDMLTRGYFDY (SEQ ID NO: 2858)
1076G11	1552	143 144 - 259	143 - 259	166 - 179	195 - 205	240 - 248	1 - 127	26 - 35	50 - 66	99 - 116	GTGYDILTGYMGSAFDQ (SEQ ID NO: 2800)
1076G12	1553	146 147 - 257	146 - 257	169 - 181	197 - 203	236 - 246	1 - 130	26 - 35	50 - 66	99 - 119	NGYYDILTGYLWDYYGMDV (SEQ ID NO: 2769)
1076H02	1554	140 141 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	ENYDSLTYGYYNFDY (SEQ ID NO: 2971)
1076H04	1555	141 143 - 251	141 - 251	165 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	THYDILTGYYSHPLDY (SEQ ID NO: 2863)
1076H05	1556	140 141 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1076H06	1557	140 141 - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 35	50 - 66	99 - 113	VPYDILTGYWGAFDV (SEQ ID NO: 2827)
1076H09	1558	143 144 - 256	143 - 256	166 - 179	195 - 201	234 - 245	1 - 127	26 - 35	50 - 66	99 - 116	PSGYDLLTYFTGSPLDY (SEQ ID NO: 2766)
1076H10	1559	143 144 - 256	143 - 256	166 - 179	195 - 201	234 - 245	1 - 127	26 - 35	50 - 66	99 - 116	SGGYDLLTYFTGSPLDY (SEQ ID NO: 2766)
1077D06	1560	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	VYYDILTGYNLFFDY (SEQ ID NO: 2177)
1078B04	1561	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	VYYDILTGYNLFFDY (SEQ ID NO: 2177)
1078E10	1562	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1002A01-K	1563	141 142 - 250	141 - 250	164 - 174	190 - 196	229 - 239	1 - 125	26 - 35	50 - 66	99 - 114	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1002A01-R	1564	141 142 - 250	141 - 250	164 - 174	190 - 196	229 - 239	1 - 125	26 - 35	50 - 66	99 - 114	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1026C04-K	1565	141 142 - 250	141 - 250	164 - 176	192 - 198	231 - 239	1 - 125	26 - 35	50 - 66	99 - 114	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1026C04-R	1566	141 142 - 250	141 - 250	164 - 176	192 - 198	231 - 239	1 - 125	26 - 35	50 - 66	99 - 114	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1067B10	1567	149 - 259	149 - 259	171 - 183	199 - 205	238 - 248	1 - 133	26 - 35	50 - 66	99 - 122	DRGAPNYDILTYYPAAQGVAFDI (SEQ ID NO: 2176)
1068C06	1568	133 134 - 244	133 - 244	156 - 169	185 - 191	224 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1075F12	1569	133 134 - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1003C06	1570	140 141 - 249	140 - 249	163 - 173	189 - 195	228 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1025B06	1571	140 141 - 249	140 - 249	163 - 175	191 - 197	230 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1025B09	1572	140 141 - 249	140 - 249	163 - 175	191 - 197	230 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1026C04	1573	140 141 - 249	140 - 249	163 - 175	191 - 197	230 - 238	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1027B12	1574	141 142 - 250	141 - 250	164 - 174	190 - 196	229 - 239	1 - 125	26 - 34	49 - 65	99 - 114	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1030A10	1575	140 141 - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1064C04	1576	147 - 257	147 - 257	169 - 182	198 - 204	237 - 246	1 - 131	26 - 35	50 - 66	99 - 120	DGRLSYDILTYGYARDYYGMDD (SEQ ID NO: 2188)
1064C07	1577	134 - 241	134 - 241	157 - 167	183 - 189	222 - 230	1 - 118	26 - 35	50 - 66	99 - 107	SEGTFGVD (SEQ ID NO: 2178)
1065D04	1578	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 36	51 - 66	99 - 117	GKGYVDILTGYRDNNWFDP (SEQ ID NO: 2181)
1065D08	1579	147 - 257	147 - 257	169 - 182	198 - 204	237 - 246	1 - 131	26 - 35	50 - 66	99 - 120	TPSSVYDILLTYHYFYSYMVDY (SEQ ID NO: 2189)
1065F08	1580	135 - 242	135 - 242	158 - 168	184 - 190	223 - 231	1 - 119	26 - 35	50 - 66	99 - 108	EKSAAGYFDY (SEQ ID NO: 2190)
1067F05	1581	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ENYDSLTYGYYGAFDI (SEQ ID NO: 2185)
1068B04	1582	133 134 - 244	133 - 244	156 - 168	184 - 190	223 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1068B08	1583	140 141 - 252	140 - 252	163 - 175	191 - 197	231 - 241	1 - 124	26 - 34	49 - 65	98 - 113	KLGLSIVGATTGALDM (SEQ ID NO: 2186)
1068C08	1584	142 143 - 254	142 - 254	165 - 178	194 - 200	233 - 243	1 - 126	26 - 35	50 - 66	99 - 115	EGMNDFFINSHHYTMDA (SEQ ID NO: 2182)
1068F03	1585	139 140 - 251	139 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	AGNEYGHTERPADY (SEQ ID NO: 2180)
1069B07	1586	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	MEYDILTGYGGYFDY (SEQ ID NO: 2179)
1071B03	1587	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTCGYSFDGFDI (SEQ ID NO: 2153)
1072B09	1588	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTCGYSFDGFDI (SEQ ID NO: 2153)
1073F04	1589	136 - 246	136 - 246	158 - 171	187 - 193	226 - 235	1 - 120	26 - 35	50 - 66	99 - 109	SLATRPLGMDV (SEQ ID NO: 2184)

1074B12	1590	140-252	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1075A02	1591	140-251	140-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGSIVGATTGALDM (SEQ ID NO: 2174)
1075G01	1592	140-251	140-251	164-174	190-196	229-240	1-124	26-35	50-66	99-113	DHFDLTGYFRRLLDS (SEQ ID NO: 2187)
1078D02	1593	140-250	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDILTGYNLFDDY (SEQ ID NO: 2177)
1078D08	1594	144-251	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	DAQSYDILTGYQSYAFDI (SEQ ID NO: 2183)
1078H08	1595	140-250	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDILTGYNLFDDY (SEQ ID NO: 2177)
1064A03	1596	150-257	150-257	171-181	197-203	236-246	1-134	26-35	50-66	99-123	GPSTTYDILTGYTPYYYYMDV (SEQ ID NO: 3014)
1064B03	1597	145-255	145-255	167-179	195-201	234-244	1-129	26-37	52-67	100-118	HVRDYDILTGYRHHYFDY (SEQ ID NO: 2167)
1064B05	1598	140-250	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113	ERGVVTA YGGDSFDL (SEQ ID NO: 2985)
1064B11	1599	138-248	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	DRPGLLSSFFES (SEQ ID NO: 3033)
1064C02	1600	146-256	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	DEYDYDILTYQAPYYGYGMDV (SEQ ID NO: 3068)
1064C03	1601	140-250	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ERGVVTA YGGDSFDL (SEQ ID NO: 2985)
1064C11	1602	143-253	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116	DVYTHDILTGYAGHEAFDI (SEQ ID NO: 3055)
1064C12	1603	148-255	148-255	171-181	197-203	236-244	1-132	26-37	52-69	102-121	ESGRYDILTGYSGGGMDV (SEQ ID NO: 3012)
1064D03	1604	146-256	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119	DGANYDILTGYTTTYYGMDV (SEQ ID NO: 3072)
1064D04	1605	141-251	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	RSYDILTGYTYGMDV (SEQ ID NO: 3090)
1064D06	1606	134-244	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107	EGSSGYLVG (SEQ ID NO: 2981)
1064E05	1607	146-256	146-256	168-180	196-202	235-245	1-130	26-37	52-67	100-119	KQRGDYDILTGYQLGYAFDI (SEQ ID NO: 2808)
1064E06	1608	145-255	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-118	ERPGYDILTGYPSIYGMDV (SEQ ID NO: 3053)
1064F07	1609	141-248	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1064F09	1610	147-257	147-257	169-181	197-203	236-246	1-131	26-35	50-66	99-120	DTLGYDILTGYPPYYYYMDV (SEQ ID NO: 2988)
1064F10	1611	143-253	143-253	165-177	193-199	232-242	1-127	22-31	46-62	95-116	DTLGYDILTGYPPYYYYMDV (SEQ ID NO: 2988)
1064F11	1612	142-252	142-252	164-177	193-199	232-241	1-126	26-35	50-65	98-115	GRHYDILTGYYNFAFDI (SEQ ID NO: 3031)
1064G01	1613	140-250	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	NYVDLTSYGYGMDV (SEQ ID NO: 3077)
1064G04	1614	133-243	133-243	155-167	183-189	222-232	1-117	26-35	50-66	99-106	DNSTGYG (SEQ ID NO: 3084)
1064G08	1615	138-245	138-245	159-169	185-191	224-234	1-122	26-35	50-66	99-111	GGVTAGRSVYFDS (SEQ ID NO: 2990)
1064G10	1616	140-250	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	SPNGDYSYAWGLE (SEQ ID NO: 3085)
1064G11	1617	138-248	138-248	160-173	189-195	228-237	1-122	26-35	50-65	98-111	YFDGSGYYPVSFSY (SEQ ID NO: 3064)
1064G12	1618	139-249	139-249	161-173	189-195	228-238	1-123	26-35	50-65	98-112	VNYDILTGLGYFFDY (SEQ ID NO: 3049)
1064H03	1619	143-253	143-253	165-178	194-200	233-242	1-127	26-37	52-67	100-116	SYDILTGRPYTDADF (SEQ ID NO: 2989)
1064H04	1620	142-249	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	PLGITAVRGAKTDAFGI (SEQ ID NO: 2929)
1064H06	1621	149-256	149-256	170-180	196-202	235-245	1-133	26-35	50-66	99-122	DRGASNYDILTGYAPAQGVAFDI (SEQ ID NO: 2969)
1065A02	1622	141-248	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065A04	1623	141-248	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065A06	1624	141-248	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065A07	1625	144-254	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DGGYDILTGYQYYGYGMDV (SEQ ID NO: 2987)
1065B01	1626	145-255	145-255	167-180	196-202	235-244	1-129	26-35	50-65	98-118	WATYDILTGYRLKDHAGFDI (SEQ ID NO: 3017)
1065B05	1627	142-252	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	SPGDDILTGYKYYFFDY (SEQ ID NO: 3032)
1065B09	1628	146-253	146-253	167-177	193-199	232-242	1-130	26-35	50-66	99-112	DAGESYDILTGYVIEGYMDV (SEQ ID NO: 2986)
1065B12	1629	139-249	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	EGAAADYLNQYFQH (SEQ ID NO: 2815)
1065C02	1630	136-246	136-246	158-170	186-192	225-235	1-120	26-35	50-66	99-109	EGSWGLDLDY (SEQ ID NO: 3007)
1065C06	1631	141-253	141-253	163-175	191-197	230-242	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)

1065C08	1632	141 - 250	141 - 250	163 - 176	192 - 198	231 - 239	1 - 125	26 - 35	50 - 66	99 - 114	VSGYNSGYFESYDMDV (SEQ ID NO: 2732)
1065C10	1633	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	QGGQYDSPPLDV (SEQ ID NO: 3002)
1065D01	1634	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	DRDYDILTGYSNYGMVDV (SEQ ID NO: 3074)
1065D03	1635	142 - 249	142 - 249	165 - 175	191 - 197	230 - 238	1 - 126	26 - 35	50 - 66	99 - 115	APLYDILTGY'GGNDV (SEQ ID NO: 3028)
1065D05	1636	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DKDYDILTYWRDELLDY (SEQ ID NO: 3040)
1065D06	1637	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	DPNYDILTGY'YYAMDV (SEQ ID NO: 3062)
1065E01	1638	139138 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	EFDQLLARGHGMVDV (SEQ ID NO: 3027)
1065E05	1639	137136 - 244	137 - 244	158 - 168	184 - 190	223 - 233	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1065E06	1640	146 - 256	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 66	99 - 119	ARGSYDILTGY'YRPGDGVFDV (SEQ ID NO: 3043)
1065E08	1641	142141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GLSYFEDTNYRHGDAFDI (SEQ ID NO: 2790)
1065E09	1642	145 - 255	145 - 255	167 - 179	195 - 201	234 - 244	1 - 129	26 - 35	50 - 65	99 - 118	ERSYYDILTGYSPRSKYGMVDV (SEQ ID NO: 3021)
1065E12	1643	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065F04	1644	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ERGVVTAYGDSFDL (SEQ ID NO: 2985)
1065F05	1645	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 65	98 - 113	RYSDALTYGSLGAFDV (SEQ ID NO: 3018)
1065F07	1646	145144 - 252	145 - 252	166 - 176	192 - 198	231 - 241	1 - 129	26 - 38	53 - 69	102 - 118	GAYYDILTGY'PYGMVDV (SEQ ID NO: 2860)
1065F09	1647	143142 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	DYPIDVLTGRRRTKNWFDP (SEQ ID NO: 3013)
1065F12	1648	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	DQVDRLLMQ'NY'YMDA (SEQ ID NO: 3047)
1065G01	1649	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1065G09	1650	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 68	101 - 116	DAYYDILTGWVYGMVDV (SEQ ID NO: 3030)
1065G10	1651	140139 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 36	51 - 66	99 - 113	FRYDILTGY'YDMVDV (SEQ ID NO: 2983)
1065H05	1652	140139 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	EYYDILTGYSGAFDI (SEQ ID NO: 2984)
1065H07	1653	138 - 248	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	99 - 111	TRMDVLT'RY'SDF (SEQ ID NO: 2750)
1066A05	1654	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMTYGTDV (SEQ ID NO: 2773)
1066A06	1655	139138 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	EGAADYLNQYFQH (SEQ ID NO: 2815)
1066A12	1656	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	DTRVIGIQLWERGAFDM (SEQ ID NO: 3080)
1066B05	1657	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1066B11	1658	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	PLGITAVRGAKTDAFGI (SEQ ID NO: 2929)
1066C06	1659	144 - 254	144 - 254	166 - 178	194 - 200	233 - 243	1 - 128	26 - 35	50 - 65	98 - 117	GRRYYDILTGYSLRGEMDV (SEQ ID NO: 3009)
1066C10	1660	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1066D02	1661	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGTSLMNYGTDV (SEQ ID NO: 3048)
1066D07	1662	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	GPYDVLTYG'LSGNFDV (SEQ ID NO: 2992)
1066E01	1663	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	QGGQYDSPFDV (SEQ ID NO: 3001)
1066E03	1664	149 - 259	149 - 259	171 - 184	200 - 206	239 - 248	1 - 133	26 - 35	50 - 66	99 - 122	GEKARYYDILTGY'SAWGGYMDV (SEQ ID NO: 3045)
1066E04	1665	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	LNLEKTVIRGFGYFDL (SEQ ID NO: 3081)
1066E05	1666	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	VGGYDILTGY'LRGMVDV (SEQ ID NO: 2997)
1066E07	1667	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1066E09	1668	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1066F01	1669	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	SPYDILTGY'VYNGVDV (SEQ ID NO: 3058)
1066F03	1670	141140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1066F04	1671	141 - 251	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	VAAAGARTLGYFGMDV (SEQ ID NO: 3071)
1066F07	1672	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DVSGHDILTGY'SRYFVDV (SEQ ID NO: 2795)
1066F08	1673	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	SPMYDRLTGFYPSGYFDS (SEQ ID NO: 3036)

1066F11	1674	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	GAYYDILTGYYPYGMVDV (SEQ ID NO: 2860)
1066F12	1675	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	GPSSAGTTIGLSFDP (SEQ ID NO: 3005)
1066G06	1676	143 142 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	ETRKYTSSPPNYYYMDV (SEQ ID NO: 2736)
1066G07	1677	133 - 243	133 - 243	155 - 168	184 - 190	223 - 232	1 - 117	26 - 30	45 - 61	94 - 106	DQFSVGGRRHFDL (SEQ ID NO: 3054)
1066H02	1678	135 134 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1066H02	1679	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1067A03	1680	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMYGTDV (SEQ ID NO: 2773)
1067A06	1681	141 140 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1067A08	1682	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMYGTDV (SEQ ID NO: 2773)
1067A10	1683	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	PLGVVTA YGGDSFDL (SEQ ID NO: 2985)
1067B03	1684	142 - 253	142 - 253	164 - 177	193 - 199	232 - 242	1 - 126	26 - 35	50 - 66	99 - 115	ELGITAVRGAKTDAFGI (SEQ ID NO: 2929)
1067B04	1685	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMYGTDV (SEQ ID NO: 2773)
1067C03	1686	133 134 - 244	133 - 244	156 - 169	185 - 191	224 - 233	1 - 117	26 - 35	50 - 66	99 - 106	DWGHWFDP (SEQ ID NO: 2982)
1067C05	1687	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	SGSSLMYGTDV (SEQ ID NO: 3015)
1067C07	1688	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	EPYDILTGYYSYFDY (SEQ ID NO: 3041)
1067C10	1689	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMYGTDV (SEQ ID NO: 2773)
1067C12	1690	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	TYYDILTGYSGGAFDY (SEQ ID NO: 3024)
1067D01	1691	136 - 246	136 - 246	158 - 171	187 - 193	226 - 235	1 - 120	26 - 35	50 - 66	99 - 109	GSRVRGVTPDL (SEQ ID NO: 3020)
1067D03	1692	137 136 - 244	137 - 244	158 - 168	184 - 190	223 - 233	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMYGTDV (SEQ ID NO: 2773)
1067D05	1693	146 - 256	146 - 256	168 - 180	196 - 202	235 - 245	1 - 130	26 - 35	50 - 66	99 - 119	ECSSGSCPARPPYYQYYMDV (SEQ ID NO: 2993)
1067D06	1694	137 136 - 244	137 - 244	158 - 168	184 - 190	223 - 233	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMYGTDV (SEQ ID NO: 2773)
1067D09	1695	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	GAYYDILTGYYPYGMVDV (SEQ ID NO: 2860)
1067D12	1696	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	QGGQYDSPPLDV (SEQ ID NO: 3002)
1067E02	1697	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMYGTDV (SEQ ID NO: 2773)
1067E04	1698	142 - 252	142 - 252	164 - 176	192 - 198	231 - 241	1 - 126	26 - 35	50 - 66	99 - 115	GAYYDILTGYYPYGMVDV (SEQ ID NO: 2860)
1067E05	1699	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DYRNYDILTGHPPYYGMDV (SEQ ID NO: 2996)
1067F01	1700	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	QHYDILTGYSQEPFDI (SEQ ID NO: 3022)
1067F03	1701	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DQTYDILTGHYYYGMDV (SEQ ID NO: 3087)
1067F04	1702	139 138 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	EGAAADYLNQYFQH (SEQ ID NO: 2815)
1067F08	1703	140 139 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	LCGYDILTGYRSDDY (SEQ ID NO: 3029)
1067F10	1704	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMAYGTDV (SEQ ID NO: 3016)
1067F11	1705	140 139 - 248	140 - 248	161 - 171	187 - 193	226 - 237	1 - 124	26 - 35	50 - 66	99 - 113	ENYDFLTGYYGAFDI (SEQ ID NO: 2772)
1067G01	1706	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1067G09	1707	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGSSLMYGTDV (SEQ ID NO: 2773)
1067H07	1708	144 143 - 251	144 - 251	165 - 175	191 - 197	230 - 240	1 - 128	26 - 35	50 - 66	99 - 117	GGLYDILTGRPATDDAFDI (SEQ ID NO: 3035)
1068A07	1709	142 143 - 254	142 - 254	165 - 178	194 - 200	233 - 243	1 - 126	26 - 35	50 - 66	99 - 115	TDRFGAKDVTARWGMDV (SEQ ID NO: 2979)
1068E05	1710	142 148 - 257	147 - 257	170 - 183	199 - 205	238 - 246	1 - 131	26 - 35	50 - 66	99 - 120	GRDRTDKVKPDRYHYYYMDV (SEQ ID NO: 2809)
1068E08	1711	133 135 - 247	133 - 247	157 - 169	185 - 193	226 - 236	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYLDL (SEQ ID NO: 2175)
1068E11	1712	140 141 - 251	140 - 251	163 - 176	192 - 198	231 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1068F04	1713	141 142 - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	ELGHRREGGYWSPYNV (SEQ ID NO: 2838)
1068G05	1714	135 137 - 245	135 - 245	159 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	98 - 108	KNMGASAAADF (SEQ ID NO: 3042)
1068G06	1715	139 140 - 250	139 - 250	162 - 174	190 - 196	229 - 239	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPPFYYYMNV (SEQ ID NO: 2755)

1068G11	1716	146-258	169-182	198-204	237-247	1-130	26-35	50-66	99-119	ESGSHYDLLTGELVAANGFDV (SEQ ID NO: 3044)
1069A09	1717	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1069A10	1718	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1069B06	1719	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1069B09	1720	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	PYYDILTGAFADI (SEQ ID NO: 3026)
1069B12	1721	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1069C06	1722	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	VLPHYDILTGYSQNWFDP (SEQ ID NO: 3000)
1069C09	1723	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	VLPHYDILTGYSQNWFDP (SEQ ID NO: 3000)
1069D03	1724	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMVDV (SEQ ID NO: 2135)
1069E09	1725	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMVDV (SEQ ID NO: 2135)
1069E11	1726	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	VYYDILTGYNLFDDV (SEQ ID NO: 2177)
1069F05	1727	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1069F07	1728	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1069F12	1729	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	GYYDILTGYYDAFDI (SEQ ID NO: 3051)
1069G06	1730	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMVDV (SEQ ID NO: 3059)
1069G08	1731	145-252	166-176	192-198	231-241	1-129	26-35	50-66	99-118	DRLEYDILTGYYYYGMVDV (SEQ ID NO: 3039)
1069G11	1732	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1070A03	1733	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1070A09	1734	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1070B01	1735	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	SQSDYDILTGYYYYGMVDV (SEQ ID NO: 3038)
1070B05	1736	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1070D03	1737	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1070D04	1738	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTSYGGYFDV (SEQ ID NO: 3034)
1070E01	1739	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	SQSDYDILTGYYYYGMVDV (SEQ ID NO: 3038)
1070F01	1740	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	SQSNYDILTGYYYYGMVDV (SEQ ID NO: 3067)
1070G10	1741	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDV (SEQ ID NO: 2179)
1071A06	1742	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	GMGDHYGMVDV (SEQ ID NO: 2161)
1071B02	1743	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-108	GMGDHYGMVDV (SEQ ID NO: 2161)
1071D02	1744	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO: 3048)
1071D08	1745	146-256	168-181	197-203	236-245	1-130	26-37	52-66	99-119	VYYDTSGGYLGYYGMVDV (SEQ ID NO: 3010)
1071F01	1746	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO: 3048)
1071G09	1747	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072A01	1748	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	SRDILLPHYGMVDV (SEQ ID NO: 2133)
1072A09	1749	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072B02	1750	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	GMGDHYGMVDV (SEQ ID NO: 2161)
1072B10	1751	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMYGTVDV (SEQ ID NO: 2773)
1072B11	1752	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072B12	1753	140-249	162-173	189-195	228-238	1-124	26-35	50-66	99-113	ENYDYLTYGYGAFDI (SEQ ID NO: 2995)
1072C05	1754	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108	GMGDHYGMVDV (SEQ ID NO: 2161)
1072C10	1755	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072D01	1756	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072D05	1757	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108	GMGDHYGMVDV (SEQ ID NO: 2161)

1072E01	1758	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072E04	1759	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EGSYDILTGYYVGVGRMDV (SEQ ID NO: 2171)
1072E05	1760	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072E06	1761	135 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1072F03	1762	135 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1072F07	1763	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072F11	1764	140 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	DEYDILTGLLQGMVDV (SEQ ID NO: 2883)
1072G03	1765	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072G04	1766	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 68	101 - 110	RDILTGFDYS (SEQ ID NO: 2933)
1072G05	1767	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	GYRNDWYGAFDI (SEQ ID NO: 3079)
1072G09	1768	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072H03	1769	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1072H07	1770	137 - 247	137 - 247	159 - 172	188 - 194	227 - 236	1 - 121	26 - 35	50 - 66	99 - 110	AGTSLMNYGMDV (SEQ ID NO: 3070)
1073A02	1771	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	GPYDILTGYYRDAFDI (SEQ ID NO: 2998)
1073A03	1772	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	THYDILTGYYTADAFDI (SEQ ID NO: 3019)
1073A04	1773	148 - 258	148 - 258	170 - 183	199 - 205	238 - 247	1 - 132	26 - 35	50 - 66	99 - 121	VQMDSEYYDLTGINVGPPYFDY (SEQ ID NO: 2132)
1073A05	1774	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073A06	1775	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073A09	1776	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073A10	1777	146 - 253	146 - 253	167 - 177	193 - 199	232 - 242	1 - 130	26 - 35	50 - 66	99 - 119	GDFGDYDILTGYYPPVYGMVDV (SEQ ID NO: 3082)
1073A11	1778	141 - 248	141 - 248	164 - 174	190 - 196	229 - 237	1 - 125	26 - 35	50 - 66	99 - 114	SYDILTGYPFGMDV (SEQ ID NO: 3004)
1073B02	1779	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DLWYYDILTGYYLDDAFDI (SEQ ID NO: 2999)
1073B05	1780	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	DLWYYDILTGYYLDDAFDI (SEQ ID NO: 2999)
1073B06	1781	139 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	SRDILLPPHYGMDV (SEQ ID NO: 2133)
1073B07	1782	138 - 248	138 - 248	160 - 173	189 - 195	228 - 237	1 - 122	26 - 35	50 - 66	99 - 111	TRMDVLTTRYSDF (SEQ ID NO: 2750)
1073B08	1783	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073B11	1784	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073C01	1785	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	GYHDTLTSYNNWFDP (SEQ ID NO: 3006)
1073C02	1786	148 - 255	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 66	99 - 121	AQMDSEYYDLTGINVGPPYFDY (SEQ ID NO: 3076)
1073C04	1787	141 - 252	141 - 252	164 - 177	193 - 199	232 - 241	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073C07	1788	134 - 241	134 - 241	155 - 165	181 - 187	220 - 230	1 - 118	26 - 35	50 - 66	99 - 107	GMGDHYGMDV (SEQ ID NO: 3008)
1073C08	1789	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 66	99 - 115	EMGYDILTGYYLNYMDV (SEQ ID NO: 2862)
1073C09	1790	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 115	QHYDILTGYSQEPFDI (SEQ ID NO: 3022)
1073C11	1791	146 - 256	146 - 256	168 - 181	197 - 203	236 - 245	1 - 130	26 - 35	50 - 68	101 - 119	FNPTYDILTGYYIGGVFQH (SEQ ID NO: 2155)
1073C12	1792	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073D01	1793	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073D03	1794	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1073D06	1795	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073D08	1796	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVRYDILTRSYLEAGPLDN (SEQ ID NO: 2751)
1073D10	1797	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 68	101 - 113	QYYDILTGVELDI (SEQ ID NO: 3073)
1073D11	1798	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073E01	1799	148 - 258	148 - 258	170 - 183	199 - 205	238 - 247	1 - 132	26 - 37	52 - 69	102 - 121	EGAHYDILTGHNYYHYGMDV (SEQ ID NO: 2747)

1073E02	1800	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073E03	1801	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 3003)
1073E05	1802	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	QHYDILTGYSQEPDI (SEQ ID NO: 3022)
1073E06	1803	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073E08	1804	140 - 250	140 - 250	162 - 175	191 - 197	230 - 239	1 - 124	26 - 35	50 - 66	99 - 113	ENYDPLTGYYGAFDI (SEQ ID NO: 2772)
1073F01	1805	141 - 251	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073F02	1806	141 - 251	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073F03	1807	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073F05	1808	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073F07	1809	141 - 251	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073F09	1810	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	GEYDILTGYPYWFDFL (SEQ ID NO: 3023)
1073F11	1811	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073F12	1812	141 - 251	141 - 251	163 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073G03	1813	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DGSYDILTGYYIDNYMDV (SEQ ID NO: 2154)
1073G04	1814	143 - 253	143 - 253	165 - 178	194 - 200	233 - 242	1 - 127	26 - 35	50 - 65	98 - 116	GEGYDILTGRLRGYGMVDV (SEQ ID NO: 3037)
1073G05	1815	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GMGDHYGMDV (SEQ ID NO: 2161)
1073G06	1816	141 - 248	141 - 248	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073G07	1817	142 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GSYYDILTGISLGMVDV (SEQ ID NO: 3063)
1073G08	1818	142 - 249	142 - 249	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	SRDLLFPHYGMDV (SEQ ID NO: 2133)
1073G09	1819	145 - 255	145 - 255	167 - 180	196 - 202	235 - 244	1 - 129	26 - 35	50 - 66	99 - 118	DRGHYDILTGYYIEPSGFDY (SEQ ID NO: 3061)
1073G10	1820	135 - 245	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GPVIGNYDY (SEQ ID NO: 2749)
1073G12	1821	142 - 252	142 - 252	164 - 177	193 - 199	232 - 241	1 - 126	26 - 35	50 - 68	101 - 115	GGMIRAREDYNYMDV (SEQ ID NO: 3083)
1073H01	1822	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073H03	1823	141 - 251	141 - 251	162 - 172	188 - 194	227 - 237	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073H05	1824	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073H06	1825	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1073H07	1826	138 - 245	138 - 245	159 - 169	185 - 191	224 - 234	1 - 122	26 - 35	50 - 66	99 - 111	TYDILTGYYFDY (SEQ ID NO: 3056)
1073H08	1827	141 - 251	141 - 251	163 - 176	192 - 198	231 - 240	1 - 125	26 - 35	50 - 66	99 - 114	ATYDPLTGYSFDFDI (SEQ ID NO: 2153)
1074A05	1828	143 - 255	143 - 255	166 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	LPPYDMLTGYYVGGGMDV (SEQ ID NO: 3050)
1074A06	1829	143 - 253	143 - 253	167 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	AKPYTDFSRGSDADAFDV (SEQ ID NO: 3065)
1074B03	1830	133 - 242	133 - 242	156 - 166	182 - 188	221 - 231	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYDL (SEQ ID NO: 2175)
1074B11	1831	140 - 251	140 - 251	162 - 175	191 - 197	230 - 240	1 - 123	26 - 35	50 - 66	99 - 112	RYGDPFYYYMNV (SEQ ID NO: 2755)
1074C07	1832	140 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1074D03	1833	141 - 251	141 - 251	165 - 175	191 - 197	230 - 240	1 - 125	26 - 35	50 - 66	99 - 114	GGYDILTGYPAEFFHP (SEQ ID NO: 2764)
1074D04	1834	133 - 246	133 - 246	156 - 169	185 - 191	224 - 235	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYDL (SEQ ID NO: 2175)
1074D05	1835	143 - 253	143 - 253	167 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	DRYYDILTKGDYYGMDV (SEQ ID NO: 3060)
1074D07	1836	150 - 262	150 - 262	173 - 186	202 - 208	241 - 251	1 - 134	26 - 35	50 - 66	99 - 123	VQGYTYDILTGWGRKRDLYGMDV (SEQ ID NO: 3069)
1074D08	1837	140 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVATTGALDM (SEQ ID NO: 2980)
1074D11	1838	138 - 249	138 - 249	161 - 174	190 - 196	229 - 238	1 - 122	26 - 35	50 - 66	99 - 111	ESEGDDYTNPFY (SEQ ID NO: 2991)
1074E05	1839	133 - 245	133 - 245	156 - 169	185 - 191	224 - 234	1 - 117	26 - 35	50 - 66	99 - 106	DQGRYDL (SEQ ID NO: 2175)
1074E07	1840	140 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 34	49 - 65	98 - 113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1074E09	1841	146 - 258	146 - 258	169 - 182	198 - 204	237 - 247	1 - 130	26 - 35	50 - 68	101 - 119	DPGNYDILTGYYYYGMDV (SEQ ID NO: 2935)

1074E11	1842	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	VRLPHHHYFMAY (SEQ ID NO: 3075)
1074H05	1843	142-254	166-178	194-200	233-243	1-126	26-35	50-66	99-115	ESSITVNPPYFYGMVDV (SEQ ID NO: 3025)
1075A03	1844	133-242	158-168	184-190	223-231	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1075A10	1845	133-244	157-169	185-191	224-233	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1075B07	1846	143-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	SPEGDYQLSSNYNWLDP (SEQ ID NO: 3011)
1075D11	1847	133-246	156-169	185-191	224-235	1-117	26-36	51-66	99-106	CKEGYNDN (SEQ ID NO: 3089)
1075D12	1848	143-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GSYDILLTGYFTGSPLDY (SEQ ID NO: 2766)
1075G02	1849	143-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	SPEGDYQLSSNYNWLDP (SEQ ID NO: 3011)
1075G09	1850	142-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115	MGHYDILTYGRHYGMVDV (SEQ ID NO: 2831)
1075G10	1851	138-250	162-174	190-196	229-239	1-122	26-35	50-66	99-111	GNVDILTYPHDL (SEQ ID NO: 3086)
1075H05	1852	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	SYDILTYGYYHTPLDY (SEQ ID NO: 2853)
1075H07	1853	143-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GSYDILLTGYFTGSPLDY (SEQ ID NO: 2766)
1076A11	1854	141-254	164-177	193-199	232-243	1-125	26-35	50-66	99-114	DDRDLTNYLYEYFQH (SEQ ID NO: 2868)
1076A12	1855	143-256	166-178	194-200	233-245	1-127	26-35	50-66	99-116	GSYDVLTYGFTGSPLDY (SEQ ID NO: 3057)
1076B06	1856	140-249	164-174	190-196	229-238	1-124	26-35	50-66	99-113	GRYDILTYGFTSFDY (SEQ ID NO: 3066)
1076B10	1857	141-254	164-177	193-199	232-243	1-125	26-35	50-66	99-114	DDRDLTNYLYEYFQH (SEQ ID NO: 2868)
1076B12	1858	143-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GTGYDILTYGYMGSAFDQ (SEQ ID NO: 2800)
1076C06	1859	142-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115	MGHYDILTYGRHYGMVDV (SEQ ID NO: 2831)
1076C11	1860	133-245	156-168	184-190	223-234	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1076D06	1861	140-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1076E05	1862	143-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	GTGYDILTYGYMGSAFDQ (SEQ ID NO: 2800)
1076E08	1863	133-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO: 2175)
1076F06	1864	133-245	156-169	185-191	224-234	1-117	26-36	51-66	99-106	RDVQGAPY (SEQ ID NO: 3088)
1076G01	1865	143-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	VEGYDILTYGSFADF (SEQ ID NO: 3078)
1076H01	1866	144-254	168-178	194-200	233-243	1-128	26-35	50-66	99-117	EQGYDILTYGYPGGWFD (SEQ ID NO: 2834)
1076H03	1867	140-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO: 2174)
1077B05	1868	147-257	169-182	198-204	237-246	1-131	26-37	52-69	102-120	DKSYDILTYGYYGMDV (SEQ ID NO: 3052)
1077C10	1869	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTYGYYGFDY (SEQ ID NO: 2179)
1077D01	1870	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTYGYYGFDY (SEQ ID NO: 2179)
1077D04	1871	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTYGYYGFDY (SEQ ID NO: 2179)
1077D11	1872	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTYGYYGFDY (SEQ ID NO: 2179)
1077D12	1873	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	EKYDILTYGYYDAFDI (SEQ ID NO: 3046)
1077E01	1874	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	EMGYDILTYGYYLNYMDV (SEQ ID NO: 2862)
1077E03	1875	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	EMGYDILTYGYYLNYMDV (SEQ ID NO: 2862)
1077E08	1876	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTYGYYGFDY (SEQ ID NO: 2179)
1077F05	1877	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTYGYYGFDY (SEQ ID NO: 2179)
1077G06	1878	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTYGYYGFDY (SEQ ID NO: 2179)
1077H02	1879	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTYGYYGFDY (SEQ ID NO: 2179)
1078B05	1880	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	ESHYDILTYGYYSNPSFDI (SEQ ID NO: 2994)
1079E02	1881	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	DSGSYYDAFDI (SEQ ID NO: 2194)
1079F11	1882	132-239	155-165	181-187	220-228	1-116	26-35	50-66	99-105	TGSGFDY (SEQ ID NO: 2192)
1082G02	1883	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	DGYRTNDALDI (SEQ ID NO: 2191)

1082H08	1884	131 132 - 242	131 - 242	154 - 167	183 - 189	222 - 231	1 - 115	26 - 35	50 - 66	99 - 104	DWDMDV (SEQ ID NO: 2193)
1099D03	1885	136 137 - 247	136 - 247	159 - 172	188 - 194	227 - 236	1 - 120	26 - 35	50 - 66	99 - 109	DNGGTIGFDY (SEQ ID NO: 2195)
1079B05	1886	130 - 240	130 - 240	152 - 165	181 - 187	220 - 229	1 - 114	26 - 35	50 - 66	99 - 103	FVLDDY (SEQ ID NO: 2210)
1079B12	1887	134 - 241	134 - 241	157 - 167	183 - 189	222 - 230	1 - 118	26 - 35	50 - 66	99 - 107	WTSSGAFDI (SEQ ID NO: 2205)
1079C01	1888	131 - 241	131 - 241	153 - 166	182 - 188	221 - 230	1 - 115	26 - 35	50 - 66	99 - 104	DWDMDV (SEQ ID NO: 2193)
1079F06	1889	134 - 241	134 - 241	157 - 167	183 - 189	222 - 230	1 - 118	26 - 35	50 - 66	99 - 107	DNLHAAFDI (SEQ ID NO: 2202)
1079F08	1890	138 - 248	138 - 248	160 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	YYYHSSGDAFDI (SEQ ID NO: 2206)
1080A03	1891	138 139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 111	VGKAAAADNFY (SEQ ID NO: 2197)
1080A08	1892	135 136 - 247	135 - 247	158 - 171	187 - 193	226 - 236	1 - 119	26 - 35	50 - 66	99 - 108	VHSTGYAFEN (SEQ ID NO: 2200)
1080B01	1893	142 144 - 254	142 - 254	166 - 178	194 - 200	233 - 243	1 - 126	26 - 35	50 - 66	99 - 115	EYSGYHYVEGGSYAMDY (SEQ ID NO: 2201)
1080D03	1894	138 139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 111	VGKAAAADNFY (SEQ ID NO: 2197)
1080E05	1895	141 142 - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	EGGGDAYDVAPYFDY (SEQ ID NO: 2204)
1080G07	1896	136 138 - 245	136 - 245	161 - 172	188 - 194	227 - 234	1 - 120	26 - 35	50 - 66	99 - 109	EGPGYYYGMDV (SEQ ID NO: 2209)
1080G09	1897	136 137 - 249	136 - 249	159 - 172	188 - 194	227 - 238	1 - 120	26 - 35	50 - 66	99 - 109	DNGGTIGFDY (SEQ ID NO: 2195)
1082A05	1898	131 - 240	131 - 240	153 - 165	181 - 187	220 - 229	1 - 115	26 - 35	50 - 66	99 - 104	DLDFDY (SEQ ID NO: 2208)
1082B08	1899	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	DLGIAGTTFDY (SEQ ID NO: 2207)
1082C03	1900	138 - 245	138 - 245	161 - 171	187 - 193	226 - 234	1 - 122	26 - 35	50 - 66	99 - 111	DASRDIVVLPAL (SEQ ID NO: 2198)
1082D07	1901	134 - 241	134 - 241	157 - 167	183 - 189	222 - 230	1 - 118	26 - 35	50 - 66	99 - 107	WTSSGAFDI (SEQ ID NO: 2205)
1082G01	1902	138 - 245	138 - 245	161 - 171	187 - 193	226 - 234	1 - 122	26 - 35	50 - 66	99 - 111	DRSGGWPWYFDL (SEQ ID NO: 2212)
1083B12	1903	137 139 - 247	137 - 247	161 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	ESGAGGYYDDY (SEQ ID NO: 2196)
1083G03	1904	138 139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 111	VGKAAAADNFY (SEQ ID NO: 2197)
1084A01	1905	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084B02	1906	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084C04	1907	131 130 - 238	131 - 238	152 - 162	178 - 184	217 - 227	1 - 115	25 - 34	49 - 65	98 - 104	NLWGLDY (SEQ ID NO: 2199)
1084C11	1908	134 - 244	134 - 244	156 - 169	185 - 191	224 - 233	1 - 118	26 - 35	50 - 66	99 - 107	GNAWGAFDI (SEQ ID NO: 2211)
1079A01	1909	134 - 243	134 - 243	156 - 168	184 - 190	223 - 232	1 - 118	26 - 35	50 - 66	99 - 107	EGVAAAGEDY (SEQ ID NO: 3123)
1079A03	1910	134 - 244	134 - 244	156 - 169	185 - 191	224 - 233	1 - 118	26 - 35	50 - 66	99 - 107	GGMDWDFDY (SEQ ID NO: 3183)
1079A04	1911	134 133 - 241	134 - 241	155 - 165	181 - 187	220 - 230	1 - 118	26 - 35	50 - 66	99 - 107	VDSSGYAYY (SEQ ID NO: 3213)
1079A06	1912	133 132 - 240	133 - 240	154 - 164	180 - 186	219 - 229	1 - 117	26 - 35	50 - 66	99 - 106	DAAVTAEG (SEQ ID NO: 3142)
1079A07	1913	136 - 246	136 - 246	158 - 170	186 - 192	225 - 235	1 - 120	26 - 35	50 - 66	99 - 109	GSNYSPPAFDI (SEQ ID NO: 3112)
1079A10	1914	148 147 - 255	148 - 255	169 - 179	195 - 201	234 - 244	1 - 132	26 - 35	50 - 68	101 - 121	LPPDLRYCDGGICPGFDWLGP (SEQ ID NO: 3163)
1079A11	1915	135 - 242	135 - 242	158 - 168	184 - 190	223 - 231	1 - 119	26 - 35	50 - 66	99 - 108	GPSYYYMAY (SEQ ID NO: 3114)
1079B02	1916	134 - 243	134 - 243	156 - 168	184 - 190	223 - 232	1 - 118	26 - 35	50 - 66	99 - 107	EGVAAAGEDY (SEQ ID NO: 3123)
1079B03	1917	136 - 246	136 - 246	158 - 170	186 - 192	225 - 235	1 - 120	26 - 35	50 - 66	99 - 109	GSNYSPPAFDI (SEQ ID NO: 3112)
1079B04	1918	130 - 240	130 - 240	152 - 165	181 - 187	220 - 229	1 - 114	26 - 35	50 - 66	99 - 103	LLSDY (SEQ ID NO: 3168)
1079B07	1919	138 137 - 245	138 - 245	159 - 169	185 - 191	224 - 234	1 - 122	26 - 35	50 - 66	99 - 111	DLSGSYFSDY (SEQ ID NO: 3193)
1079B09	1920	139 - 246	139 - 246	162 - 172	188 - 194	227 - 235	1 - 123	26 - 35	50 - 66	99 - 112	VEWEDIVVGSADF (SEQ ID NO: 3128)
1079C02	1921	144 - 251	144 - 251	167 - 177	193 - 199	232 - 240	1 - 128	26 - 35	50 - 66	99 - 117	VTLSYSSSGGYYYGMDV (SEQ ID NO: 3145)
1079C04	1922	132 - 239	132 - 239	155 - 165	181 - 187	220 - 228	1 - 116	26 - 35	50 - 66	99 - 105	GWRGVSDY (SEQ ID NO: 3195)
1079C05	1923	140 - 247	140 - 247	163 - 173	189 - 195	228 - 236	1 - 124	26 - 35	50 - 66	99 - 113	AGGNPRSGSLVYFDY (SEQ ID NO: 3225)
1079C07	1924	137 136 - 244	137 - 244	158 - 168	184 - 190	223 - 233	1 - 121	26 - 35	50 - 66	99 - 110	GLDVYAIYGLDV (SEQ ID NO: 3176)
1079D01	1925	144 - 254	144 - 254	166 - 179	195 - 201	234 - 243	1 - 128	26 - 35	50 - 66	99 - 117	EVARNYDLLTRSYLAGPLDN (SEQ ID NO: 2751)

1079D02	1926	135 - 245	135 - 245	157 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 66	99 - 108	EIGWEGAFDI (SEQ ID NO: 3178)
1079D04	1927	133 - 243	133 - 243	155 - 167	183 - 189	222 - 232	1 - 117	26 - 35	50 - 66	99 - 106	VRPGLMDV (SEQ ID NO: 3132)
1079D06	1928	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	EAYTSSWAEFDF (SEQ ID NO: 3190)
1079D07	1929	<u>136</u> 135 - 243	<u>136</u> 135 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	NITPLAMVGDF (SEQ ID NO: 3146)
1079D08	1930	130 - 240	130 - 240	152 - 165	181 - 187	220 - 229	1 - 114	26 - 35	50 - 66	99 - 103	LIEDF (SEQ ID NO: 3161)
1079D09	1931	<u>131</u> 130 - 238	131 - 238	152 - 162	178 - 184	217 - 227	1 - 115	26 - 35	50 - 66	99 - 104	DSGSPD (SEQ ID NO: 3108)
1079D11	1932	134 - 241	134 - 241	157 - 167	183 - 189	222 - 230	1 - 118	26 - 35	50 - 66	99 - 107	EGVAAGEDY (SEQ ID NO: 3123)
1079E06	1933	136 - 244	136 - 244	158 - 168	184 - 190	223 - 233	1 - 120	26 - 35	50 - 66	99 - 109	EKRGRRVFDI (SEQ ID NO: 3093)
1079E08	1934	137 - 247	137 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	EAYASSWAEFDF (SEQ ID NO: 3189)
1079E11	1935	136 - 243	136 - 243	159 - 169	185 - 191	224 - 232	1 - 120	26 - 35	50 - 66	99 - 109	PYGGSYAFDI (SEQ ID NO: 3185)
1079E12	1936	143 - 253	143 - 253	165 - 177	193 - 199	232 - 242	1 - 127	26 - 35	50 - 66	99 - 116	ARDYYDSSGYVPDAFDI (SEQ ID NO: 3107)
1079F01	1937	<u>133</u> 132 - 241	133 - 241	154 - 164	180 - 186	219 - 230	1 - 117	26 - 35	50 - 66	99 - 106	GHPYGMVDV (SEQ ID NO: 3098)
1079F02	1938	<u>148</u> 147 - 253	148 - 253	169 - 179	195 - 201	234 - 242	1 - 132	26 - 35	50 - 68	101 - 121	LPPDLRYCDGGMCSGFDWLGP (SEQ ID NO: 3219)
1079F03	1939	<u>140</u> 139 - 247	140 - 247	161 - 171	187 - 193	226 - 236	1 - 124	26 - 35	50 - 66	99 - 113	ESLLTEEYCGSDCYS (SEQ ID NO: 3115)
1079F04	1940	<u>136</u> 135 - 243	136 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	NSAPPAPMDV (SEQ ID NO: 3099)
1079F09	1941	<u>130</u> 129 - 237	130 - 237	151 - 161	177 - 183	216 - 226	1 - 114	26 - 35	50 - 66	99 - 103	RYYDY (SEQ ID NO: 3139)
1079F10	1942	<u>136</u> 135 - 243	136 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	NITPLAMVGDF (SEQ ID NO: 3146)
1079F12	1943	136 - 243	136 - 243	159 - 169	185 - 191	224 - 232	1 - 120	26 - 35	50 - 66	99 - 109	ADYNDYYMDV (SEQ ID NO: 3166)
1079G02	1944	<u>136</u> 135 - 243	136 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	NITPLAMVGDF (SEQ ID NO: 3146)
1079G05	1945	136 - 243	136 - 243	159 - 169	185 - 191	224 - 232	1 - 120	26 - 35	50 - 66	99 - 109	FPLESYYMDV (SEQ ID NO: 3124)
1079G06	1946	135 - 245	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	GNSFGRITLDY (SEQ ID NO: 3158)
1079H05	1947	<u>136</u> 135 - 243	136 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	DVPPPDGYLEV (SEQ ID NO: 3192)
1079H06	1948	134 - 241	134 - 241	157 - 167	183 - 189	222 - 230	1 - 118	26 - 35	50 - 66	99 - 107	ASYPVPFDY (SEQ ID NO: 3171)
1080A01	1949	<u>131</u> 132 - 242	131 - 242	154 - 166	182 - 188	221 - 231	1 - 115	26 - 35	50 - 66	99 - 104	GGWLDD (SEQ ID NO: 3210)
1080A02	1950	<u>133</u> 134 - 245	133 - 245	156 - 169	185 - 191	224 - 234	1 - 117	26 - 35	50 - 66	99 - 106	EHSSFDY (SEQ ID NO: 3111)
1080A05	1951	<u>141</u> 142 - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	EGEGDGYNVAPYYFDY (SEQ ID NO: 3160)
1080A06	1952	<u>141</u> 143 - 250	141 - 250	166 - 176	192 - 198	231 - 239	1 - 125	26 - 35	50 - 66	99 - 114	EAGGSGSYHFSFPFDY (SEQ ID NO: 3188)
1080A07	1953	<u>135</u> 136 - 247	135 - 247	158 - 171	187 - 193	226 - 236	1 - 119	26 - 35	50 - 66	99 - 108	TGIWGYFDY (SEQ ID NO: 3175)
1080A10	1954	<u>141</u> 142 - 252	141 - 252	164 - 176	192 - 198	231 - 241	1 - 125	26 - 35	50 - 66	99 - 114	DGNLYDGSSTDYGMVDV (SEQ ID NO: 3140)
1080B02	1955	<u>138</u> 140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	LGRNYTSSWSLDY (SEQ ID NO: 3181)
1080B03	1956	<u>138</u> 139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 110	LGVARGREAFDL (SEQ ID NO: 3096)
1080B05	1957	<u>137</u> 139 - 249	137 - 249	161 - 173	189 - 195	232 - 243	1 - 126	26 - 37	52 - 69	102 - 115	AVRSPGYYYYYMDV (SEQ ID NO: 3125)
1080B06	1958	<u>142</u> 143 - 254	142 - 254	165 - 177	193 - 199	232 - 243	1 - 117	26 - 35	50 - 66	99 - 106	GRKPLFDY (SEQ ID NO: 3141)
1080B07	1959	<u>133</u> 135 - 243	133 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 37	52 - 67	100 - 109	KQRREKYFDY (SEQ ID NO: 3100)
1080B08	1960	<u>136</u> 137 - 248	136 - 248	159 - 172	188 - 194	227 - 237	1 - 120	26 - 37	52 - 67	99 - 115	EKAIIETTSGEADPDI (SEQ ID NO: 3151)
1080B09	1961	<u>142</u> 143 - 254	142 - 254	165 - 178	194 - 200	233 - 243	1 - 126	26 - 35	50 - 66	100 - 111	RPALRSLWYFDL (SEQ ID NO: 3102)
1080B10	1962	<u>138</u> 139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 37	52 - 67	101 - 110	LHCTGSCGF (SEQ ID NO: 3186)
1080B11	1963	<u>137</u> 138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 68	99 - 112	NYYYDSSEGFDDY (SEQ ID NO: 3109)
1080B12	1964	<u>139</u> 141 - 253	139 - 253	164 - 179	195 - 201	234 - 242	1 - 123	26 - 35	50 - 66	99 - 111	SGRQAYYYGMDV (SEQ ID NO: 3091)
1080C03	1965	<u>138</u> 140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 117	DYYDSSSSGDDYYYYMDV (SEQ ID NO: 3227)
1080C06	1966	<u>144</u> 146 - 254	144 - 254	168 - 178	194 - 200	233 - 243	1 - 128	26 - 36	51 - 66	99 - 117	DSDLVVIPTAIQGRYYFDN (SEQ ID NO: 3113)
1080C07	1967	<u>144</u> 145 - 256	144 - 256	167 - 180	196 - 202	235 - 245	1 - 128	26 - 35	50 - 66		

1080C08	1968	137 138 - 249	137 - 249	160 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 110	CKRYSYGWYFDI (SEQ ID NO: 3130)
1080C10	1969	131 132 - 243	131 - 243	154 - 167	183 - 189	222 - 232	1 - 115	26 - 35	50 - 66	99 - 104	DTPLDP (SEQ ID NO: 3094)
1080C11	1970	137 138 - 249	137 - 249	160 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 110	EGDPTDNDAPDV (SEQ ID NO: 3155)
1080C12	1971	138 139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 111	DGPTYARPYLDH (SEQ ID NO: 3153)
1080D01	1972	136 138 - 245	136 - 245	161 - 171	187 - 193	226 - 234	1 - 120	26 - 35	50 - 66	99 - 109	DGTKYDWGFDY (SEQ ID NO: 3220)
1080D02	1973	141 142 - 254	141 - 254	164 - 177	193 - 199	232 - 243	1 - 125	26 - 35	50 - 66	99 - 114	ETFSHCSCGYPFYD (SEQ ID NO: 3212)
1080D04	1974	138 140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	SGRQAYYYYGMDV (SEQ ID NO: 3091)
1080D05	1975	136 138 - 246	136 - 246	160 - 170	186 - 192	225 - 235	1 - 120	26 - 35	50 - 66	99 - 109	EFFGYVYLTDY (SEQ ID NO: 3165)
1080D08	1976	137 138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 68	101 - 110	LHCTGGSCGF (SEQ ID NO: 3186)
1080D09	1977	138 139 - 250	138 - 250	161 - 174	190 - 196	229 - 239	1 - 122	26 - 35	50 - 66	99 - 111	VDYTDYEMGAFEI (SEQ ID NO: 3187)
1080D11	1978	135 136 - 247	135 - 247	158 - 171	187 - 193	226 - 236	1 - 119	26 - 35	50 - 66	99 - 108	VGNFGYYFEY (SEQ ID NO: 3196)
1080D12	1979	135 137 - 245	135 - 245	159 - 169	185 - 191	224 - 234	1 - 119	26 - 35	50 - 68	101 - 108	SSRNGGDY (SEQ ID NO: 3214)
1080E01	1980	136 138 - 246	136 - 246	160 - 170	186 - 192	225 - 235	1 - 120	26 - 35	50 - 66	99 - 109	DLRSVAGRFDY (SEQ ID NO: 3164)
1080E04	1981	136 137 - 247	136 - 247	159 - 171	187 - 193	226 - 236	1 - 120	26 - 37	52 - 67	100 - 109	HDVYGDLDY (SEQ ID NO: 3211)
1080E06	1982	137 138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 68	101 - 110	LHCSGGSCGF (SEQ ID NO: 3221)
1080E07	1983	142 143 - 254	142 - 254	165 - 178	194 - 200	233 - 243	1 - 126	26 - 35	50 - 66	99 - 115	EGSIVGATLTINDAFDI (SEQ ID NO: 3150)
1080E08	1984	137 138 - 249	137 - 249	160 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 110	CKRYSYGWYFDI (SEQ ID NO: 3130)
1080E12	1985	130 132 - 242	130 - 242	154 - 166	182 - 188	221 - 231	1 - 114	26 - 35	50 - 66	99 - 103	DPFDY (SEQ ID NO: 3134)
1080F04	1986	138 139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 111	DGPTYARPYLDH (SEQ ID NO: 3153)
1080F05	1987	142 143 - 253	142 - 253	165 - 177	193 - 199	232 - 242	1 - 126	26 - 35	50 - 66	99 - 115	ESSGTLGEFSLELPDY (SEQ ID NO: 3203)
1080F06	1988	138 140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	LGRNYTSSWSLDY (SEQ ID NO: 3181)
1080F08	1989	140 142 - 250	140 - 250	164 - 174	190 - 196	229 - 239	1 - 124	26 - 36	51 - 66	99 - 103	NAFDY (SEQ ID NO: 3121)
1080G03	1990	131 133 - 244	131 - 244	156 - 171	187 - 193	226 - 233	1 - 115	26 - 35	50 - 66	99 - 113	GRGYSSSSVYGMDI (SEQ ID NO: 3095)
1080G04	1991	143 145 - 252	143 - 252	167 - 177	193 - 199	232 - 241	1 - 127	26 - 35	50 - 66	99 - 104	VHSSGS (SEQ ID NO: 3216)
1080G10	1992	136 137 - 247	136 - 247	159 - 171	187 - 193	226 - 236	1 - 120	26 - 37	52 - 67	99 - 116	KRGDFGVIRLHHYYGMDV (SEQ ID NO: 3136)
1080G11	1993	140 142 - 252	140 - 252	164 - 176	192 - 198	231 - 241	1 - 124	26 - 37	52 - 67	100 - 109	HDVYGDLDY (SEQ ID NO: 3205)
1080H01	1994	139 140 - 248	139 - 248	162 - 172	188 - 194	227 - 237	1 - 123	26 - 35	50 - 66	100 - 113	LRPDADYGDYGFYD (SEQ ID NO: 3218)
1080H02	1995	135 136 - 246	135 - 246	158 - 170	186 - 192	225 - 235	1 - 119	26 - 35	50 - 66	99 - 112	TSEGTYYRQWDFDN (SEQ ID NO: 3204)
1080H03	1996	137 138 - 249	137 - 249	160 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 108	EAGEVAADY (SEQ ID NO: 3180)
1080H04	1997	136 137 - 247	136 - 247	159 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	CKRYSYGWYFDI (SEQ ID NO: 3130)
1080H05	1998	137 138 - 249	137 - 249	160 - 173	189 - 195	228 - 238	1 - 120	26 - 35	50 - 66	100 - 109	HDVYGDLDY (SEQ ID NO: 3205)
1080H06	1999	137 138 - 249	137 - 249	160 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 66	99 - 110	LHCTGGSCGF (SEQ ID NO: 3186)
1080H07	2000	137 138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 68	101 - 110	ERGRDGDYALDF (SEQ ID NO: 3148)
1080H08	2001	138 140 - 251	138 - 251	162 - 175	191 - 197	230 - 240	1 - 122	26 - 35	50 - 66	99 - 111	RTPDHNGDSGPPDY (SEQ ID NO: 3215)
1080H09	2002	139 141 - 249	139 - 249	163 - 173	189 - 195	228 - 238	1 - 123	26 - 36	51 - 66	99 - 112	ESLTGGAFDI (SEQ ID NO: 3117)
1081A01	2003	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081A03	2004	135 - 245	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	ESLTGGAFDI (SEQ ID NO: 3117)
1081A04	2005	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081A06	2006	130 129 - 237	130 - 237	151 - 161	177 - 183	216 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081A08	2007	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081A09	2008	134 133 - 241	134 - 241	155 - 165	181 - 187	220 - 230	1 - 118	26 - 35	50 - 66	99 - 107	GAGSRYFDL (SEQ ID NO: 3118)
1081A10	2009	133 - 243	133 - 243	155 - 168	184 - 190	223 - 232	1 - 117	26 - 35	50 - 66	99 - 106	GGDRAFDI (SEQ ID NO: 3119)

1081B01	2010	130129 - 236	130 - 236	151 - 161	177 - 183	216 - 225	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081B04	2011	134 - 244	134 - 244	156 - 169	185 - 191	224 - 233	1 - 118	26 - 35	50 - 66	99 - 107	GNAWGAFDI (SEQ ID NO: 2211)
1081B05	2012	133 - 243	133 - 243	155 - 168	184 - 190	223 - 232	1 - 117	26 - 35	50 - 66	99 - 106	GGDRAFDI (SEQ ID NO: 3119)
1081B06	2013	133132 - 240	133 - 240	154 - 164	180 - 186	219 - 229	1 - 117	26 - 35	50 - 66	99 - 106	VKRYFYDY (SEQ ID NO: 3179)
1081B07	2014	136135 - 243	136 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	ELTGANDAFDI (SEQ ID NO: 3104)
1081B08	2015	132131 - 239	132 - 239	153 - 163	179 - 185	218 - 228	1 - 116	26 - 35	50 - 66	99 - 105	RRYALDY (SEQ ID NO: 2920)
1081B09	2016	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081B10	2017	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081B11	2018	132131 - 239	132 - 239	153 - 163	179 - 185	218 - 228	1 - 116	26 - 35	50 - 66	99 - 105	GFALYKD (SEQ ID NO: 3169)
1081C07	2019	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081C08	2020	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081D04	2021	135134 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	EDLTGDAFDI (SEQ ID NO: 3103)
1081D06	2022	132131 - 239	132 - 239	153 - 163	179 - 185	218 - 228	1 - 116	26 - 35	50 - 66	99 - 105	GDAYFDY (SEQ ID NO: 3147)
1081D08	2023	132131 - 239	132 - 239	153 - 163	179 - 185	218 - 228	1 - 116	26 - 35	50 - 66	99 - 105	GDAYFDY (SEQ ID NO: 3147)
1081D09	2024	130 - 238	130 - 238	152 - 162	178 - 184	217 - 227	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081D10	2025	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081D11	2026	134 - 244	134 - 244	156 - 169	185 - 191	224 - 233	1 - 118	26 - 35	50 - 66	99 - 107	EGLDADFID (SEQ ID NO: 3200)
1081D12	2027	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081E02	2028	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081E03	2029	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081E05	2030	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081E06	2031	134133 - 241	134 - 241	155 - 165	181 - 187	220 - 230	1 - 118	26 - 35	50 - 66	99 - 107	VGYGKGDDY (SEQ ID NO: 3137)
1081E07	2032	134133 - 241	134 - 241	155 - 165	181 - 187	220 - 230	1 - 118	26 - 35	50 - 66	99 - 107	GAGSRYFDL (SEQ ID NO: 3118)
1081E10	2033	142141 - 249	142 - 249	163 - 173	189 - 195	228 - 238	1 - 126	26 - 35	50 - 66	99 - 115	GLAPIVDGGMNDADFID (SEQ ID NO: 3184)
1081F01	2034	130 - 239	130 - 239	152 - 164	180 - 186	219 - 228	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081F04	2035	132131 - 239	132 - 239	153 - 163	179 - 185	218 - 228	1 - 116	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081F05	2036	130129 - 237	130 - 237	151 - 161	177 - 183	216 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081F06	2037	134 - 244	134 - 244	156 - 169	185 - 191	224 - 233	1 - 118	26 - 35	50 - 66	99 - 107	ERGNQAFDI (SEQ ID NO: 3156)
1081F07	2038	132131 - 239	132 - 239	153 - 163	179 - 185	218 - 228	1 - 116	26 - 35	50 - 66	99 - 105	RRYALDY (SEQ ID NO: 2920)
1081F11	2039	130129 - 237	130 - 237	151 - 161	177 - 183	216 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081G01	2040	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081G04	2041	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081G06	2042	135 - 245	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	SRSPYDAFDI (SEQ ID NO: 3097)
1081G10	2043	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081H02	2044	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081H03	2045	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1081H04	2046	135134 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	SNWGGDAFDI (SEQ ID NO: 3202)
1081H06	2047	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	LAFDI (SEQ ID NO: 3174)
1081H08	2048	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1082A02	2049	139 - 249	139 - 249	161 - 173	189 - 195	228 - 238	1 - 123	26 - 35	50 - 66	99 - 112	PAASSRGPKDAFDI (SEQ ID NO: 3129)
1082A04	2050	130 - 240	130 - 240	152 - 165	181 - 187	220 - 229	1 - 114	26 - 35	50 - 66	99 - 103	LSGDS (SEQ ID NO: 3122)
1082A08	2051	134 - 243	134 - 243	156 - 168	184 - 190	223 - 232	1 - 118	26 - 35	50 - 66	99 - 107	EGVAAAGEDY (SEQ ID NO: 3123)

1082A11	2052	130 - 240	130 - 240	152 - 165	181 - 187	220 - 229	1 - 114	26 - 35	50 - 66	99 - 103	FVL DY (SEQ ID NO: 2210)
1082B06	2053	131 - 238	131 - 238	154 - 164	180 - 186	219 - 227	1 - 115	26 - 35	50 - 66	99 - 104	GN GKDV (SEQ ID NO: 3135)
1082B09	2054	134 - 241	134 - 241	157 - 167	183 - 189	222 - 230	1 - 118	26 - 35	50 - 66	99 - 107	EGV AAGED Y (SEQ ID NO: 3123)
1082B12	2055	131 - 241	131 - 241	153 - 166	182 - 188	221 - 230	1 - 115	26 - 35	50 - 66	99 - 104	DLDFY (SEQ ID NO: 2208)
1082C01	2056	<u>136</u> 135 - 243	136 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	VNDIVVDM DV (SEQ ID NO: 3143)
1082C05	2057	<u>136</u> 135 - 243	136 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	EKRGSRRVFDI (SEQ ID NO: 3093)
1082C08	2058	<u>137</u> 136 - 244	137 - 244	158 - 168	184 - 190	223 - 233	1 - 121	26 - 35	50 - 66	99 - 110	LSNRDNLRLDY (SEQ ID NO: 3106)
1082D02	2059	130 - 240	130 - 240	152 - 165	181 - 187	220 - 229	1 - 114	26 - 35	50 - 66	99 - 103	FVL DY (SEQ ID NO: 2210)
1082E05	2060	<u>134</u> 133 - 241	134 - 241	155 - 165	181 - 187	220 - 229	1 - 118	26 - 35	50 - 66	99 - 107	TWATNTFDM (SEQ ID NO: 3152)
1082E06	2061	130 - 240	130 - 240	152 - 165	181 - 187	220 - 229	1 - 114	26 - 35	50 - 66	99 - 103	FDL DY (SEQ ID NO: 3167)
1082E07	2062	139 - 246	139 - 246	162 - 172	188 - 194	227 - 235	1 - 123	26 - 35	50 - 66	99 - 112	VEWEDIVVGSADF (SEQ ID NO: 3128)
1082F11	2063	136 - 243	136 - 243	159 - 169	185 - 191	224 - 232	1 - 120	26 - 35	50 - 66	99 - 109	GGDMITVT TDY (SEQ ID NO: 3177)
1082G07	2064	136 - 243	136 - 243	159 - 169	185 - 191	224 - 232	1 - 120	26 - 35	50 - 66	99 - 109	ADYSNDYYMDV (SEQ ID NO: 3166)
1082G10	2065	<u>134</u> 138 - 249	134 - 249	160 - 173	189 - 195	228 - 238	1 - 118	26 - 35	50 - 66	99 - 107	EGV AAGED Y (SEQ ID NO: 3123)
1082G11	2066	<u>143</u> 142 - 250	143 - 250	164 - 174	190 - 196	229 - 239	1 - 127	26 - 35	50 - 66	99 - 116	GPYYFDGSA YEGYYFDY (SEQ ID NO: 3222)
1082H04	2067	<u>131</u> 131 - 238	132 - 238	153 - 163	179 - 185	218 - 227	1 - 116	26 - 35	50 - 65	98 - 105	MNADAFEI (SEQ ID NO: 3223)
1082H09	2068	<u>139</u> 138 - 246	139 - 246	160 - 170	186 - 192	225 - 235	1 - 123	26 - 35	50 - 66	99 - 112	PAASSRGP KDAFDI (SEQ ID NO: 3129)
1083A06	2069	<u>136</u> 137 - 244	136 - 244	159 - 169	185 - 191	224 - 233	1 - 120	26 - 35	50 - 66	99 - 109	DSRPTNRAFHY (SEQ ID NO: 3110)
1083A09	2070	<u>137</u> 138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 68	101 - 110	LHCTGGSCGF (SEQ ID NO: 3186)
1083A11	2071	<u>135</u> 136 - 248	135 - 248	158 - 171	187 - 193	226 - 237	1 - 119	26 - 35	50 - 66	99 - 108	VRDDSAGFDY (SEQ ID NO: 3173)
1083B03	2072	<u>137</u> 139 - 247	137 - 247	161 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	VLVRGQYRGMDL (SEQ ID NO: 3138)
1083B05	2073	<u>138</u> 139 - 250	138 - 250	161 - 174	190 - 196	229 - 239	1 - 122	26 - 35	50 - 66	99 - 111	VDYTDYEMGAFDL (SEQ ID NO: 3172)
1083B06	2074	<u>138</u> 139 - 250	138 - 250	161 - 174	190 - 196	229 - 239	1 - 122	26 - 35	50 - 66	99 - 111	DRIAAAGGDAFDI (SEQ ID NO: 3194)
1083B10	2075	<u>137</u> 139 - 246	137 - 246	162 - 172	188 - 194	227 - 235	1 - 121	26 - 35	50 - 66	99 - 110	DLYKNGYALFDS (SEQ ID NO: 3197)
1083C01	2076	<u>135</u> 136 - 247	135 - 247	158 - 171	187 - 193	226 - 236	1 - 119	26 - 35	50 - 66	99 - 108	DEYSSLYMDV (SEQ ID NO: 3201)
1083C02	2077	<u>136</u> 136 - 246	135 - 246	158 - 171	187 - 193	226 - 235	1 - 119	26 - 35	50 - 66	99 - 108	FGAGRLYDDY (SEQ ID NO: 3224)
1083C07	2078	<u>136</u> 137 - 249	136 - 249	159 - 172	188 - 194	227 - 238	1 - 120	26 - 35	50 - 66	99 - 109	DNGGTIGFDY (SEQ ID NO: 2195)
1083C12	2079	<u>135</u> 136 - 246	135 - 246	158 - 171	187 - 193	226 - 235	1 - 119	26 - 35	50 - 66	99 - 108	DQGIETANDY (SEQ ID NO: 3207)
1083D04	2080	<u>145</u> 146 - 256	145 - 256	168 - 181	197 - 203	236 - 245	1 - 129	26 - 35	50 - 66	99 - 118	DILPDYDFWPNEDASSLDT (SEQ ID NO: 3133)
1083D07	2081	<u>148</u> 150 - 262	148 - 262	173 - 188	204 - 210	243 - 251	1 - 132	26 - 35	50 - 66	99 - 121	DFQMVRGVFIANPPYYNYGMDV (SEQ ID NO: 3154)
1083D08	2082	<u>142</u> 143 - 254	142 - 254	165 - 178	194 - 200	233 - 243	1 - 126	26 - 35	50 - 66	99 - 115	DADGLVEAETTNWFDS (SEQ ID NO: 3126)
1083D10	2083	<u>146</u> 147 - 258	146 - 258	169 - 181	197 - 203	236 - 247	1 - 130	26 - 37	52 - 69	102 - 119	ATKSYDILTRMYYYHMDV (SEQ ID NO: 2748)
1083D12	2084	<u>132</u> 134 - 242	132 - 242	156 - 166	182 - 188	221 - 231	1 - 116	26 - 35	50 - 66	99 - 105	DRTRMDV (SEQ ID NO: 3182)
1083E02	2085	<u>138</u> 139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 111	VGKAAAVDNFEY (SEQ ID NO: 2197)
1083E03	2086	<u>135</u> 136 - 248	135 - 248	158 - 171	187 - 193	226 - 237	1 - 119	26 - 35	50 - 66	99 - 108	DEIYNDAFY (SEQ ID NO: 3105)
1083E04	2087	<u>143</u> 144 - 255	143 - 255	166 - 179	195 - 201	234 - 244	1 - 127	26 - 35	50 - 66	99 - 116	DGDISPINNQNYAMD (SEQ ID NO: 3101)
1083E08	2088	<u>138</u> 140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	RGGTSENYS GMDV (SEQ ID NO: 3209)
1083E12	2089	<u>134</u> 135 - 245	134 - 245	157 - 170	186 - 192	225 - 234	1 - 118	26 - 35	50 - 66	99 - 107	DYPHNAFDI (SEQ ID NO: 3127)
1083F02	2090	<u>145</u> 146 - 258	145 - 258	168 - 181	197 - 203	236 - 247	1 - 129	26 - 35	50 - 66	99 - 118	DYRSDRFWSGQFYHSGMDV (SEQ ID NO: 3131)
1083F04	2091	<u>137</u> 138 - 248	137 - 248	160 - 172	188 - 194	227 - 237	1 - 121	26 - 35	50 - 66	99 - 110	STLEVGA TDFDY (SEQ ID NO: 3199)
1083F06	2092	<u>134</u> 135 - 247	134 - 247	157 - 170	186 - 192	225 - 236	1 - 118	26 - 35	50 - 66	99 - 107	SDDWGAYHI (SEQ ID NO: 3198)
1083F08	2093	<u>138</u> 139 - 250	138 - 250	161 - 174	190 - 196	229 - 239	1 - 122	26 - 35	50 - 66	99 - 111	ERGRDGDYALDF (SEQ ID NO: 3148)

1083F11	2094	136137 - 248	136 - 248	159 - 172	188 - 194	227 - 237	1 - 120	26 - 35	50 - 66	99 - 109	ELVAPGCFDP (SEQ ID NO: 3191)
1083G04	2095	138139 - 250	138 - 250	161 - 174	190 - 196	229 - 239	1 - 122	26 - 35	50 - 66	99 - 111	VDYTDYEMGAFDL (SEQ ID NO: 3172)
1083G05	2096	137139 - 249	137 - 249	161 - 173	189 - 195	228 - 238	1 - 121	26 - 35	50 - 68	101 - 110	SVAGRGNFYD (SEQ ID NO: 3208)
1083G06	2097	138139 - 250	138 - 250	161 - 174	190 - 196	229 - 239	1 - 122	26 - 35	50 - 66	99 - 111	EGGRDGDYALDF (SEQ ID NO: 3148)
1083G08	2098	141142 - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	EGGGDAYDVAPYYFDY (SEQ ID NO: 2204)
1083G09	2099	130132 - 242	130 - 242	154 - 166	182 - 188	221 - 231	1 - 114	26 - 35	50 - 66	99 - 103	DPFDY (SEQ ID NO: 3134)
1083G11	2100	140141 - 252	140 - 252	163 - 176	192 - 198	231 - 241	1 - 124	26 - 35	50 - 66	99 - 113	ALLGLPSDFSYVVDV (SEQ ID NO: 3159)
1083H04	2101	141142 - 253	141 - 253	164 - 177	193 - 199	232 - 242	1 - 125	26 - 35	50 - 66	99 - 114	EGEGDGYNVAPYYFDY (SEQ ID NO: 3160)
1083H05	2102	133135 - 243	133 - 243	157 - 167	183 - 189	222 - 232	1 - 117	26 - 35	50 - 66	99 - 106	TDYGGFDY (SEQ ID NO: 3092)
1083H07	2103	137139 - 247	137 - 247	161 - 171	187 - 193	226 - 236	1 - 121	26 - 35	50 - 66	99 - 110	GGVGDSRGVFPD (SEQ ID NO: 3162)
1084A03	2104	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084A08	2105	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084B08	2106	135134 - 242	135 - 242	156 - 166	182 - 188	221 - 231	1 - 119	26 - 35	50 - 66	99 - 108	ESLTGDAFDI (SEQ ID NO: 3116)
1084C02	2107	136135 - 243	136 - 243	157 - 167	183 - 189	222 - 232	1 - 120	26 - 35	50 - 66	99 - 109	SPLHFSDAFDI (SEQ ID NO: 3120)
1084D03	2108	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084D05	2109	133 - 243	133 - 243	155 - 168	184 - 190	223 - 232	1 - 117	26 - 35	50 - 66	99 - 106	EVGGAFDI (SEQ ID NO: 3157)
1084E01	2110	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084E06	2111	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084E10	2112	130129 - 237	130 - 237	151 - 161	177 - 183	216 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084E12	2113	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084F04	2114	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084F07	2115	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084F12	2116	135 - 245	135 - 245	157 - 170	186 - 192	225 - 234	1 - 119	26 - 35	50 - 66	99 - 108	ESLTGDAFDI (SEQ ID NO: 3116)
1084G12	2117	130 - 240	130 - 240	152 - 164	180 - 186	219 - 229	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1084H02	2118	130 - 237	130 - 237	153 - 163	179 - 185	218 - 226	1 - 114	26 - 35	50 - 66	99 - 103	DTTDDY (SEQ ID NO: 2203)
1099B05	2119	145146 - 256	145 - 256	168 - 180	196 - 202	235 - 245	1 - 129	26 - 35	50 - 66	99 - 118	GAHYDRSPSHLKSYYWYFDL (SEQ ID NO: 3149)
1099G09	2120	138139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 111	VGIKAAAVDNFEY (SEQ ID NO: 2197)
1099H01	2121	138140 - 248	138 - 248	162 - 172	188 - 194	227 - 237	1 - 122	26 - 35	50 - 66	99 - 111	LGRNYTSSWLDY (SEQ ID NO: 3181)
1099H06	2122	138139 - 249	138 - 249	161 - 173	189 - 195	228 - 238	1 - 122	26 - 35	50 - 66	99 - 111	VGIKAAAVDNFEY (SEQ ID NO: 2197)
1099H08	2123	144145 - 255	144 - 255	167 - 179	195 - 201	234 - 244	1 - 128	26 - 35	50 - 66	99 - 117	GGRYGYVDGTGYVDAFDI (SEQ ID NO: 3226)
1100A01	2124	136137 - 247	136 - 247	159 - 172	188 - 194	227 - 236	1 - 120	26 - 35	50 - 66	99 - 109	DNGGTTIGFDY (SEQ ID NO: 2195)
1100A10	2125	140141 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	VRQJIADPPRSFFDP (SEQ ID NO: 3144)
1100B03	2126	136137 - 247	136 - 247	159 - 172	188 - 194	227 - 236	1 - 120	26 - 35	50 - 66	99 - 109	DNGGTTIGFDY (SEQ ID NO: 2195)
1100B04	2127	136137 - 247	136 - 247	159 - 172	188 - 194	227 - 236	1 - 120	26 - 35	50 - 66	99 - 109	DNGGTTIGFDY (SEQ ID NO: 2195)
1100C03	2128	140141 - 251	140 - 251	163 - 175	191 - 197	230 - 240	1 - 124	26 - 35	50 - 66	99 - 113	VRQJIADPPRSFFDP (SEQ ID NO: 3144)

ABSTRACT

The present invention relates to antibodies and related molecules that immunospecifically bind to BLySB Lymphocyte Stimulator. The present invention also relates to methods and compositions for detecting or diagnosing a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression or inappropriate function of BLySB Lymphocyte Stimulator comprising antibodies or fragments or variants thereof or related molecules that immunospecifically bind to BLySB Lymphocyte Stimulator. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant BLySB Lymphocyte Stimulator expression or inappropriate BLySB Lymphocyte Stimulator function comprising administering to an animal an effective amount of one or more antibodies or fragments or variants thereof or related molecules that immunospecifically bind to BLySB Lymphocyte Stimulator.